Proceedings From the Cutaneous Lymphoma Summit 2009

Guest Editors: Stuart R. Lessin, MD; Pierluigi Porcu, MD

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The Proceedings of the Cutaneous Lymphoma Summit 2009: A Dedication

Marie-France Demierre
March 6, 1967 - April 13, 2010

The Board of Directors of the Cutaneous Lymphoma Foundation, along with colleagues and co-editors for this Supplement to The Journal of Clinical Lymphoma, Myeloma & Leukemia, Stuart Lessin, MD and Pierluigi Porcu, MD, dedicate this journal supplement to the legacy and memory of Marie-France Demierre, MD, FRCPC, Director of Skin Oncology, Boston School of Medicine.

Dr. Demierre passed away suddenly on April 13, 2010 and is missed greatly by her clinical colleagues, her friends at the Cutaneous Lymphoma Foundation, her grateful patients, and her loving family. She was a passionate advocate for patient care, an internationally acknowledged expert in cutaneous lymphomas, and a bright, vivacious woman with thousands of admirers and friends around the world.

Dr. Demierre’s collaboration with the Cutaneous Lymphoma Foundation was both professional and personal. Her landmark work, with the help of the Foundation, in delineating the impact of cutaneous lymphomas on patients and the resultant publication in CANCER gave needed additional credence to the goals of the Foundation. Her dedicated work and her collaborative relationships were energized by her effervescent personality and her flair for high-spirited discovery. It is in this spirit that she will remain with the Foundation and inspire us every day to make sure every patient with cutaneous lymphoma gets the best care possible.

Contributions to the Cutaneous Lymphoma Foundation in Dr. Demierre’s memory may be sent to: Cutaneous Lymphoma Foundation, PO Box 374, Birmingham, MI 48012
Donations may also be made at www.clfoundation.org.
For The Fight Against cutaneous T-cell lymphoma (CTCL)

ONTAK tactical™ TREATMENT

ONTAK is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor.

Please see inside spread for Boxed WARNINGS and additional Important Safety Information.

ONTAK®
(denileukin diftitox)

PROVEN PERFORMANCE

DENILEUKIN DIFTITOX INCLUDED IN THE MF/SS NCCN GUIDELINES FOR APPROVED INDICATION.¹
ONTAK Proven Performance in the Fight Against CTCL

Exhibited Significant Efficacy

**STUDY 1:**
- ORR for all ONTAK patients dosed 18 mcg/kg/day or 9 mcg/kg/day was approximately 42%²
- 67% of study patients ≤ stage II²

*Adjusted for disease stage and changes in randomization ratios.

STUDY 2:
- 30% OR (CCR+CR+PR) for all stages (95% CI, 18%-41%)²
- Of the patients who responded, one-third were stage 1B (7/21, 33%)²

Study 2 Design²: A randomized, double-blind, phase III study evaluating doses of 18 or 9 mcg/kg/day of ONTAK in 71 patients with recurrent or persistent stage IB to IVA CTCL.

Infusion Reactions

Infusion reactions, defined as symptoms occurring within 24 hours of infusion and resolving within 48 hours of the last infusion in that course, were reported in 70.5% of 234 ONTAK-treated patients across 3 clinical studies. Serious infusion reactions were reported in 8.1% of patients. There have been post-marketing reports of infusion reactions resulting in death.

**IMPORTANT SAFETY INFORMATION**

The following adverse events have been reported:
- Serious and fatal infusion reactions. Administer ONTAK in a facility equipped and staffed for cardiopulmonary resuscitation. Immediately stop and permanently discontinue ONTAK for serious infusion reactions.
- Capillary leak syndrome resulting in death. Monitor weight, edema, blood pressure and serum albumin levels prior to and during ONTAK treatment.
- Loss of visual acuity and color vision.

For patients completing at least 4 courses of ONTAK treatment in a placebo-controlled trial, the incidence of infusion reactions was lower in the third and fourth cycles as compared to the first and second cycles of ONTAK.

Capillary Leak Syndrome

Capillary leak syndrome was defined as the occurrence of at least 2 of the following 3 symptoms (hypotension, edema, serum albumin <3.0 g/dL) at any time during ONTAK therapy. These symptoms were not required to occur simultaneously to be characterized as capillary leak syndrome. As defined, capillary leak syndrome was reported in 32.5% (76/234) of ONTAK-treated patients in clinical studies; one-third required hospitalization or medical intervention to prevent hospitalization. There are post-marketing reports of capillary leak syndrome resulting in death. The onset of symptoms in patients with capillary leak syndrome may be delayed, occurring up to 2 weeks following infusion. Symptoms may persist or worsen after the cessation of ONTAK.
MINIMAL MYELOSUPPRESSION

- ONTAK's side-effect profile shows minimal incidences of drug-related hematologic toxicity\(^3\)
  - Minimal incidences of anemia, neutropenia, or thrombocytopenia

IMPORTANT SAFETY INFORMATION (CONTINUED)

Regularly assess patients for weight gain, new onset or worsening edema and hypotension (including orthostatic changes). Monitor serum albumin levels prior to each course of therapy and more often as clinically indicated. Withhold ONTAK for serum albumin levels less than 3 g/dL.

**Visual Loss**

Loss of visual acuity, usually with loss of color vision, with or without retinal pigment mottling has been reported following administration of ONTAK. Recovery was reported in some of the affected patients; however, most patients reported persistent visual impairment.

**Hepatobiliary Disorders**

Increase in ALT/AST from baseline occurred in 84% of ONTAK-treated patients. The majority of these elevations occurred during either the first or second cycle, resolved without medical intervention, and did not require discontinuation of ONTAK.

Pregnancy and Lactation

ONTAK should be given to a pregnant woman only if clearly needed and should not be used in women who are nursing.

Most Common Adverse Reactions

In clinical studies (n=234), the most common adverse reactions in ONTAK-treated patients (≥20%) were pyrexia, nausea, fatigue, rigors, vomiting, diarrhea, headache, peripheral edema, cough, dyspnea and pruritus. The most common serious adverse reactions were capillary leak syndrome (11.1%), infusion reactions (8.1%), and visual changes including loss of visual acuity (4%). ONTAK was discontinued in 28.2% (66/234) of patients due to adverse reactions.

Please see Brief Summary on reverse including Boxed WARNINGS and additional Important Safety Information.

**References:**

WARNING: SERIOUS INFUSION REACTIONS, CAPILLARY LEAK SYNDROME AND LOSS OF VISUAL ACUITY.

The following adverse reactions have been reported:

- Serious and fatal infusion reactions. Administer ONTAK in a facility equipped and staffed for cardiopulmonary resuscitation. Immediately stop and permanently discontinue ONTAK for serious infusion reactions. [see Warnings and Precautions].
- Capillary leak syndrome resulting in death. Monitor weight, edema, blood pressure and serum albumin levels prior to and during ONTAK treatment. [see Warnings and Precautions].
- Loss of visual acuity and color vision. [see Warnings and Precautions].

INDICATIONS AND USAGE

ONTAK® is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor. [see Warnings and Precautions].

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion Reactions: Infusion reactions, defined as symptoms occurring within 24 hours of infusion and resolving within 48 hours of start of infusion (Waning and Precipitation), were reported in 70.3% (165/234) of ONTAK-treated patients across 3 clinical studies utilizing the approved doses and schedule. Serious infusion reactions were reported in 8.1% (19/234) of ONTAK-treated patients. There have been post-marketing reports of infusion reactions resulting in death. For patients completing at least 4 courses of ONTAK treatment in Study 1 [see Clinical Studies], the incidence of infusion reactions was lower in the 3rd and 4th cycles as compared to the 1st and 2nd cycles of ONTAK. Resuscitative equipment should be available during ONTAK administration. Immediately stop and permanently discontinue ONTAK for serious infusion reactions.

Capillary Leak Syndrome: Capillary leak syndrome was defined as the occurrence of at least 2 of the following 3 symptoms: hypotension, edema, serum albumin <30 g/dL at any time during ONTAK therapy. These symptoms were not required to occur simultaneously to be characterized as capillary leak syndrome. As defined, capillary leak syndrome was reported in 32.5% (76/234) of ONTAK-treated patients. Among these 76 patients with capillary leak syndrome, 62 required hospitalization or medical intervention to prevent hospitalization. These were post-marketing reports of capillary leak syndrome resulting in death. The onset of symptoms in patients with capillary leak syndrome may be delayed, occurring up to 2 weeks following infusion. Symptoms may persist or worsen after the cessation of ONTAK. Regularly assess patients for weight gain, new onset or worsening edema, hypotension (including orthostatic changes) and monitor serum albumin levels prior to the initiation of each course of therapy and more often as clinically indicated. Without ONTAK for serum albumin levels of less than 3.0 g/dL. [see Warnings and Precautions].

Visual Loss: Loss of visual acuity, usually with loss of color vision, with or without retinal pigment mottling has been reported following administration of ONTAK. Recovery was reported in some of the affected patients; however, most patients reported persistent visual impairment.

C205 Tumor Expression and Evaluation: Confirm that the patient’s malignant cells express C205 prior to administration of ONTAK. A testing service for the assay of C205 expression in tumor biopsy samples is available. For information on this service call 877-873-4724.

Laboratory Monitoring/Hypoalbuminemia: Monitor serum albumin levels prior to the initiation of each treatment course. Withhold administration of ONTAK if serum albumin levels are less than 3.0 g/dL. [see Dosage and Administration and Warnings and Precautions].

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Infusion Reactions [see Warnings and Precautions]
- Capillary Leak Syndrome [see Warnings and Precautions]
- Visual Loss [see Warnings and Precautions]

CLINICAL STUDIES EXPERIENCE

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data are available for 3 clinical studies in which 234 patients received ONTAK at 9 mcg/kg (n=80) or 18 mcg/kg (n=154) at the recommended schedule. Of these studies, 1 was placebo-controlled and dose-ranging (Study 1, 100 ONTAK-treated patients), 1 was a dose-escalation control (Study 2, n=71), and the third was a single-arm study using 18 mcg/kg (n=66); all studies were limited to adult patients with CTCL. The median age of patients across the clinical studies was 60 years (range 23-91 years) and 36% (n=65) were 65 years of age or older; 55% were men and 85% were Caucasian.

Across all 3 studies, the most common adverse reactions in ONTAK-treated patients (≥20%) were pyrexia, nausea, fatigue, rigor, vomiting, diarrhea, headache, peripheral edema, cough, dyspnea, and pruritus. The most common serious adverse reactions were capillary leak syndrome (11.1%), infusion reactions (8.1%), and visual changes including loss of visual acuity (4%). ONTAK was discontinued in 28.2% (66/234) of patients due to adverse reactions.

The data described in Table 1 reflect exposure to ONTAK in 100 patients administered as a single agent at the recommended dosing schedule in the randomized placebo-controlled trial (Study 1). The median number of ONTAK cycles was 7 (range 1-10) for the 9 mcg/kg cohort and 6 (range 1-11) for the 18 mcg/kg cohort. The median age of patients across the clinical studies was 60 years (range 23-91 years) and 36% (n=65) were 65 years of age or older; 55% were men and 86% were Caucasian.

Table 1: Incidence of Adverse Reactions Occurring in ≥10% of ONTAK-treated patients (18 mcg/kg group) and at a higher rate than Placebo in Study 1

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>MedReA version 6.1</th>
<th>Placebo</th>
<th>ONTAK 9 mcg/kg</th>
<th>ONTAK 18 mcg/kg</th>
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<tr>
<td>Pyrexia</td>
<td>7 (15.9)</td>
<td>22 (48.8)</td>
<td>35 (63.6)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (22.7)</td>
<td>21 (46.7)</td>
<td>33 (58.0)</td>
<td></td>
</tr>
<tr>
<td>Rigors</td>
<td>9 (20.0)</td>
<td>19 (42.2)</td>
<td>26 (47.3)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (31.8)</td>
<td>21 (46.2)</td>
<td>24 (43.6)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (6.8)</td>
<td>6 (13.3)</td>
<td>19 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>8 (18.2)</td>
<td>13 (28.9)</td>
<td>14 (25.5)</td>
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Hepatobiliary Disorders: Increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) from baseline occurred in 84% of subjects treated with ONTAK (197/234). In the majority of subjects, these enzyme elevations occurred during either the first or the second cycle; enzyme elevation resolved without medical intervention and did not require discontinuation of ONTAK.

Immunogenicity: An immune response to denileukin diftitox was assessed using 2 enzyme-linked immunosassays (ELISA). The first assay measured reactivity directed against intact denileukin diftitox calibrated against anti-diphtheria toxin, and the second assay measured reactivity against the LI-2 portion of the protein. An additional in vitro cell-based assay that measured the ability of antibodies in serum to protect a human IL-2- expressing cell line from toxicity by denileukin diftitox, was used to detect the presence of neutralizing antibodies which inhibited functional activity. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to the intact fusion protein denileukin diftitox. These results are highly dependent on the sensitivity and the specificity of the assays. Additionally, the observed incidence of the antibody positivity may be influenced by several factors, including sample handling, concomitant medication, and underlying disease. For these reasons, the comparison of the incidence of antibodies to denileukin diftitox with the incidence of antibodies to other products may be misleading. In Study 1 (see Clinical Studies), of 95 patients treated with denileukin diftitox, 66% tested positive for antibodies at baseline probably due to a prior exposure to diphtheria toxin or its vaccine. After 1, 2, and 3 courses of treatment, 94%, 99%, and 100% of patients tested positive, respectively. Mean titers of antidenileukin diftitox antibodies were similar across the 9 and 18 mcg/kg/day dose groups after 2 courses of treatment. Meanwhile, pharmacokinetic parameters decreased substantially (Gmean = 57%, AUC = 80%), and clearance increased 2- to 8-fold. In Study 2 (see Clinical Studies), 131 patients were assessed for binding antibodies. Of these, 51 patients (39%) had antibodies at baseline. Seventy-six percent of patients tested positive after 1 course of treatment and 97% after 3 courses of treatment. Neutralizing antibodies were assessed in 60 patients; 40%, 73%, and 97% had evidence of inhibited response in the cell kill assay at baseline and after 1 and 3 courses of treatment, respectively.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of ONTAK.

Gastrointestinal Disorders: nausea, vomiting, fever, chills, and/or persistent asthenia.

DRUG INTERACTIONS:

No formal drug-drug interaction studies have been conducted with ONTAK.

USE IN SPECIFIC POPULATIONS:

Pregnancy: It is not known whether ONTAK can cause fetal harm when administered to a pregnant woman or can affect reproductive ability. Animal reproduction studies have not been conducted with ONTAK. ONTAK should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether ONTAK is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ONTAK, a decision should be made whether to discontinue nursing or to discontinue ONTAK, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Clinical studies of ONTAK did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

OVERDOSAGE:

Doses of approximately twice the recommended dose (31 mcg/kg/day) resulted in moderate-to-severe nausea, vomiting, fever, chills, and/or persistent asthenia.

PATIENT COUNSELING INFORMATION

Advise patients to report:

- Fever, chills, breathing problems, chest pain, tachycardia, and urticaria following infusion
- Rapid weight gain, edema, and orthostatic hypotension following infusion. Instruct patients to weigh themselves daily.
- Visual loss, including loss of color vision

Please see package insert for full Prescribing Information.

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Cutaneous Lymphoma Summit 2009

Cutaneous Lymphoma Summit 2009 was held in New York City on October 9-11, 2009. The idea for the Summit was generated three years ago by the leadership of the Cutaneous Lymphoma Foundation, whose vision was that the cutaneous lymphoma community would benefit from an inclusive gathering to identify unifying issues important to all stakeholders. This vision is captured in the Summit’s tagline: “community, cooperation, cure.”

The major goal of the Summit was to serve as a forum for the discussion of bold ideas, explore controversial or poorly developed areas of research, and spark lively discussion among leading investigators from both within and outside the field. We hoped to broaden the cutaneous lymphoma community’s scientific horizons and enhance the application of new concepts in immunology, genetics, pharmacology, and imaging.

The Cutaneous Lymphoma Foundation is grateful to the leadership of the United States Cutaneous Lymphoma Consortium (USCLC), the International Society of Cutaneous Lymphomas (ISCL), and the Cutaneous Lymphoma Working Group of the European Organization for Research and Treatment of Cancer (EORTC) for their participation in the program.

The following pages present critical topics addressed by faculty who participated in the Summit. This issue also contains an editorial by the Summit’s scientific program co-chairs, Drs. Stuart Lessin and Pierluigi Porcu. It serves as a white paper that identifies important needs and opportunities in research, clinical care, and education. These represent strategic targets to be rapidly tackled by the cutaneous lymphoma community and to be reassessed annually for progress. It is my hope that these proceedings and white paper will spark the creation of a more collaborative research community and that its emergent ideas and commitments will garner greater attention and resources from the public sphere, thus offering greater hope to patients and families.

My gratitude and thanks are extended to all who contributed to Cutaneous Lymphoma Summit 2009 and these proceedings.

Judy Jones

Special thanks and recognition is extended to the Cutaneous Lymphoma Foundation Board of Directors and staff whose vision, collaboration, and support played a vital role in bringing these proceedings to fruition:

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Foreword

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## Translating Discovery in Cutaneous Lymphomas

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Multidisciplinary Care in Cutaneous Lymphoma

S106 Multidisciplinary Care in the Management of Patients With Cutaneous Lymphoma: A Perspective
Youn H. Kim

S109 A Look at the National Comprehensive Cancer Network Guidelines for Cutaneous Lymphomas
Pierluigi Porcu
Selected Important Safety Information

Pulmonary embolism and deep vein thrombosis have been reported. Monitor patients for pertinent signs and symptoms, particularly in patients with a history of thromboembolic events.

Treatment with ZOLINZA can cause dose-related thrombocytopenia and anemia. If platelet counts and/or hemoglobin are reduced during treatment, modify the dose or discontinue therapy.

Gastrointestinal (GI) disturbances (eg, nausea, vomiting, and diarrhea) may require antiemetics, antidiarrheals, and fluid and electrolyte replacement to prevent dehydration. Adequately control preexisting GI disturbances before beginning therapy with ZOLINZA.

Based on reports of dehydration as a serious drug-related adverse event in clinical trials, instruct patients to drink at least 2 L/day of fluids for adequate hydration.

Hyperglycemia has been observed. Monitor serum glucose, especially in diabetic or potentially diabetic patients. Adjustment of diet, therapy for increased glucose, or both may be necessary to prevent hyperglycemia.

Monitor electrolytes at baseline and periodically during treatment. Hyperkalemia or hypomagnesemia should be corrected before administering ZOLINZA.

Severe thrombocytopenia and GI bleeding have been reported with concomitant use of ZOLINZA and other HDAC inhibitors (eg, valproic acid). Monitor platelet count every 2 weeks for the first 2 months.

Carefully monitor patients concurrently administered ZOLINZA and coumarin derivatives for prolongation of prothrombin time and international normalized ratio.

The most common adverse events observed in clinical trials with ZOLINZA, regardless of causality, were fatigue (52%), diarrhea (52%), nausea (41%), dysgeusia (28%), thrombocytopenia (26%), anorexia (24%), decreased weight (21%), and muscle spasms (20%).

The most common serious adverse events, regardless of causality, were pulmonary embolism (4.7%), squamous cell carcinoma (3.5%), and anemia (2.3%).

ZOLINZA can cause fetal harm when administered to a pregnant woman. It is not known whether ZOLINZA is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug.

ZOLINZA was not evaluated in patients with hepatic impairment. Because ZOLINZA is predominantly eliminated through metabolism, treat patients with hepatic impairment with caution.

ZOLINZA is a histone deacetylase (HDAC) inhibitor indicated for treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent, or recurrent disease on or following 2 systemic therapies.

Please see the Brief Summary of Prescribing Information on the adjacent page. For copies of the Prescribing Information, call 800-672-6372, visit zolinza.com, or contact your Merck representative.

ZOLINZA is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Copyright © 2010 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. All rights reserved. 21002706(1)(602)-ZOL zolinza.com
GI disturbances, including nausea, vomiting, and diarrhea, have been reported in patients treated with ZOLINZA. The dose should be modified or therapy discontinued. [See Dosage and Administration (2.3) in the Prescribing Information, Warnings and Precautions, and Adverse Reactions.]

Hematologic events should be monitored, especially in patients with a prior history of thromboembolic disease, as pulmonary embolism and deep vein thrombosis have been reported as adverse reactions. Physicians should be alert to the signs and symptoms of these events, particularly in patients with a prior history of thromboembolic disease. A thrombocytopenia, anemia, and/or neutropenia should be monitored, especially in diabetic or potentially diabetic patients. Adjustment of diet and/or therapy for increased glucose, hypokalemia, or hypomagnesemia should be considered prior to administration of ZOLINZA, and consideration should be given to monitoring potassium and magnesium in symptomatic patients (eg, patients with nausea, vomiting, diarrhea, fluid imbalance, or cardiac symptoms).

Other Histiocytic Dystrophy (HDAC) Inhibitors
Other histiocytic dystrophy and SI bleeding have been reported with concomitant use of ZOLINZA and other HDAC inhibitors (eg, valproic acid). Monitor platelet count every 2 weeks during the first 2 months. [See Drug Interactions.]

Pregnancy
Pregnancy Category D
ZOLINZA can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ZOLINZA in pregnant women. Results of animal studies indicate that vorinostat crosses the placenta and is found in fetal plasma at levels of up to 50% of maternal concentrations. Doses of up to 50 and 150 mg/kg/day were tested in rats and rabbits, respectively (<0.5 times the human exposure based on AUC—>). Treatment-related developmental effects included decreased mean life weight; incomplete ossifications of the skull, thoracic vertebrae, and sternum; and skeletal variations (cervical rib, supernumerary rib, vertebral count, and sacral arch variations) in rats at the highest dose of vorinostat tested. Reductions in mean life weight and an elevated incidence of incomplete ossification of the metacarpals were seen in rabbits dosed at 150 mg/kg/day. The no-observed-effect levels for these findings were 15 and 50 mg/kg/day (<1.1 times the human exposure based on AUC) in rats and rabbits, respectively. A dose-related increase in the incidence of malformations of the reproductive tract was seen in all drug treatment groups in rabbits as the concurrent control. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

ADVERSE REACTIONS

The most common drug-related adverse reactions can be classified into 4 symptom complexes: GI symptoms (diarrhea, nausea, anorexia, weight decrease, vomiting, constipation), constitutional symptoms (fatigue, chills), hematologic abnormalities (thrombocytopenia, anemia), and taste disorders (dysgeusia, dry mouth). The most common serious drug-related adverse reactions were pulmonary embolism and anemia.

Clinical Trials Experience
The safety of ZOLINZA was evaluated in 107 CTCL patients in 2 single-arm clinical studies in which 86 patients received 400 mg once daily.

The data described below reflect exposure to ZOLINZA 400 mg once daily in the 86 patients for a median number of 97.5 days on therapy (range: 2–480+ days). Seventeen (19.8%) patients were exposed beyond 24 weeks and 8 (9.3%) patients were exposed beyond 3 years. The population of CTCL patients included aged 37 to 83 years; 47.7% female and 52.3% male; and 81.4% white, 16.3% black, and 1.2% Asian or multiracial. Because clinical trials are conducted under widely varying conditions, adverse-reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Common Adverse Reactions
Table 1 (top of next column) summarizes the frequency in CTCL patients of specific adverse events, regardless of causality, using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, v 3.0). The frequencies of more severe thrombocytopenia, anemia (see Warnings and Precautions), and fatigue were increased at doses higher than 400 mg once daily of ZOLINZA.

Serious Adverse Reactions
The most common serious adverse events, regardless of causality, in the 86 CTCL patients in 2 clinical studies were pulmonary embolism reported in 4.7% (4/86) of patients, squamous cell carcinoma reported in 3.5% (3/86) of patients, and anemia reported in 2.3% (2/86) of patients. There were single events of cholecystitis, death (of unknown cause), deep vein thrombosis, enterococcal infection, idiopathic dermatitis, G1 hemorrhage, infection, lobar pneumonia, myocardial infarction, ischemic stroke, pelviureteric obstruction, sepsis, spinal cord injury, streptococcal bacteremia, syncope, C1-fibrinogen, thrombocytopenia, and uterine obstruction.

Discontinuation
Of the CTCL patients who received the 400-mg once-daily dose, 9.3% (8/86) of patients discontinued ZOLINZA due to adverse events. These adverse events, regardless of causality, included anemia, angioedema, asthma, chest pain, peripheral edema, death, deep vein thrombosis, ischemic stroke, lethargy, pulmonary embolism, and spinal cord injury.

Dose Modifications
Of the CTCL patients who received the 400-mg once-daily dose, 10.5% (9/86) of patients required a dose modification of ZOLINZA due to adverse events. These adverse events included increased serum creatinine, decreased appetite, hypokalemia, leukopenia, nausea, neutropenia, thrombocytopenia, and vomiting. The median time to the first adverse event resulting in dose reduction was 42 days (range: 11–263 days).

Laboratory Abnormalities
Laboratory abnormalities were reported in all of the 86 CTCL patients who received the 400-mg once-daily dose. Increased serum glucose was reported as a laboratory abnormality in 69/86 (80%) of CTCL patients who received the 400-mg once-daily dose; only 4 of these abnormalities were severe (Grade 3). Increased serum glucose was reported as an adverse event in 8.1% (7/86) of CTCL patients who received the 400-mg once-daily dose. [See Warnings and Precautions.]

Transient increases in serum creatinine were detected in 46.5% (40/86) of CTCL patients who received the 400-mg once-daily dose. Of these laboratory abnormalities, 34 were NCI CTCAE Grade 1, 5 were Grade 2, and 1 was Grade 3. Proteinuria was detected as a laboratory abnormality (51.4%) in 38 of 74 patients tested. The clinical significance of this finding is unknown.

Dehydration
Based on reports of dehydration as a serious drug-related adverse event in clinical trials, patients were instructed to drink at least 2 L/day of fluids for adequate hydration. [See Warnings and Precautions.]

Adverse Reactions in Non-CTCL Patients
The frequencies of individual adverse events were substantially higher in the non-CTCL population. Drug-related serious adverse events reported in the non-CTCL population which were not observed in the CTCL population included simple events of blurred vision, asthma, hyperammonemia, tumor hemorrhage, Guillain-Barré syndrome, renal failure, urinary retention, cough, hemoptysis, hypertension, and vasculitis.

DRUG INTERACTIONS
Coumarin-Derivative Anticoagulants
Prolongation of prothrombin time (PT) and international normalized ratio (INR) were observed in patients receiving ZOLINZA concomitantly with coumarin-derivative anticoagulants. Physicians should carefully monitor PT and INR in patients concurrently administered ZOLINZA and coumarin derivatives.

Other HDAC Inhibitors
Serum creatinine and blood glucose have been reported with concomitant use of ZOLINZA and other HDAC inhibitors (eg, valproic acid). Monitor platelet count every 2 weeks during the first 2 months. [See Warnings and Precautions.]

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category D [See Warnings and Precautions]
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ZOLINZA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness of ZOLINZA in pediatric patients have not been established.

Geriatric Use
Of the total number of patients with CTCL in trials (n = 107), 46% were aged 65 years and over, whereas 15% were aged 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Use in Patients With Hepatic Impairment
Vorinostat was not evaluated in patients with hepatic impairment. As vorinostat is predominantly eliminated through metabolism, patients with hepatic impairment should be treated with caution. [See Clinical Pharmacology (12.3) in the Prescribing Information.]

CANTING ILLNOSUATION INFORMATION
[See FDA-Approved Patient Labeling]

Use in Patients With Renal Impairment
Patients should be instructed to drink at least 2 L/day of fluid to prevent dehydration and should promptly report excessive vomiting or diarrhea to their physician. Patients should be instructed about the signs of deep vein thrombosis and should consult their physician should any evidence of deep vein thrombosis develop. Patients receiving ZOLINZA should seek immediate medical attention if unusual bleeding occurs. ZOLINZA capsules should not be opened or crushed. Patients should be instructed to read the patient insert carefully.
The State of Cutaneous Lymphomas: A Call to Action

Introduction

Population-based and single-institution surveys from diverse geographic areas have consistently shown that in about 25%-40% of cases, malignant lymphomas originate from and exclusively progress or relapse within extranodal sites, with the skin and the gastrointestinal system representing the most common sites. The biology and clinical features of extranodal lymphomas are clearly distinct from those of lymphomas arising from the lymph nodes, and their etiology is different. For example, specific microbial triggers for extranodal B-cell lymphoma have been demonstrated. Therefore, diagnostic workup, treatment, assessment of relapse, and overall outcome are distinct from nodal lymphomas. Furthermore, the study of the development of cellular immune surveillance and of the mechanisms regulating lymphocyte homing to these critical areas of host-environment interfacing hold the key to understanding how these malignancies arise and progress.

In the skin, lymphomas may originate from B cells, T cells, or natural killer (NK) cells, reflecting a significant heterogeneity in causation. However, unlike most other extranodal sites, T-cell rather than B-cell lymphomas are the most frequent and prevalent. Hypotheses about the reasons for this observation should be informed by features of T-cell immune surveillance and environmental exposures that are unique to the skin and different from the gastrointestinal and respiratory tract. Analysis of the specific functional features of malignant T cells in cutaneous lymphoma, such as antigen receptor use, cytokine and chemokine expression, and transcriptional profile, might provide clues to the etiological agent(s), as they have in other T-cell disorders.

While a complete histogenetic and biologic characterization of primary cutaneous lymphomas has not been developed, we anticipate that future classifications schemes will be based on cell lineage, functional subset, molecular abnormalities, and clinical features, along the lines of the most current World Health Organization classification. It is conceivable that in the near future, old eponyms will be discarded in favor of more specific disease definitions. Finally, although historically the clinical and laboratory work on cutaneous lymphomas has mostly focused on the T-cell subsets, there is increasing awareness that a lack of knowledge about B-cell and NK-cell lymphomas is impairing the ability of physicians to counsel patients about risk factors, plans of care, and prognosis. One of the purposes of the Cutaneous Lymphoma Summit 2009, as reflected in the articles included in this issue, is to shed some initial light on this understudied subset of cutaneous lymphomas.

The generic term cutaneous T-cell lymphomas (CTCLs) encompasses a spectrum of T-cell malignancies that include mycosis fungoides (MF), Sézary syndrome (SS), anaplastic large-cell lymphoma, and other rare subsets. In this article, we use the general term CTCL to discuss MF/SS. An estimated 2000 new cases of CTCL are diagnosed annually, with approximately 20,000 affected in the United States, more frequently affecting the elderly and black populations. Cutaneous T-cell lymphoma typically presents with scaly patches or thickened plaques of skin that often evolve from chronic dermatoses, years before biopsy confirmation. Disease progression from early clinical stages is variable, but the burden of chronic skin disease is constant. Increasing areas of skin surface involvement are accompanied by tumor formation, ulceration, and exfoliation (erythroderma), often complicated by infections and debilitation. Advanced stages are defined by extracutaneous involvement of lymph nodes, peripheral blood, and viscera. Sézary syndrome, a triad of generalized exfoliative erythroderma, peripheral blood involvement, and lymphadenopathy, is a common presentation of advanced-stage CTCL. Prognosis of CTCL is related to the extent of skin involvement and stage at the time of diagnosis. While early-stage CTCL treated with skin-directed (nonsystemic) therapies is associated with long-term survival, advance stages have a median survival of 2.5-5.0 years, depending on the degree of extracutaneous involvement.

Cutaneous T-cell lymphoma, and all primarily cutaneous lymphomas, have now been unequivocally shown to be clinically and biologically distinct from its nodal counterparts, leading to the recognition that management of these malignancies requires a specialized approach. Over the past decade, there has been an increasing focus on cutaneous lymphomas from a variety of sectors, including academic, drug development, and patient advocacy. Professional societies and organizations have updated and revised cutaneous lymphoma classification, staging criteria, and consensus treatment guidelines. Pharmaceutical and biotechnology companies have developed new classes of therapeutic agents active in cutaneous lymphomas, such as targeted immunotoxins, retinoids, dihydrofolate reductase inhibitors, and histone deacetylase inhibitors.

The Cutaneous Lymphoma Foundation (CLF) currently serves as the largest nonprofit organization devoted to the advocacy of patients with cutaneous lymphomas (www.clfoundation.org).
Through its programs and services, it reaches patients in over 60 countries. Its mission, to ensure the best care possible for all persons diagnosed with cutaneous lymphoma, was born from their experience of navigating a health care system in search of reliable information, expert care, and hope. Their journey reflects the multi-specialty fragmentation of resources associated with cutaneous lymphomas and galvanized the need to create a more collaborative multidisciplinary community involved in research, clinical care, and advocacy. In response, the CLF sponsored and hosted the Cutaneous Lymphoma Summit 2009 in New York City, October 9-11, 2009. It was an inclusive meeting of all stakeholders (patients and families, nurses, social workers, physicians, and scientists from different disciplines) and intended to identify unifying issues and the development of a roadmap for addressing the critical needs of the cutaneous lymphoma community with emphasis on multidisciplinary collaborations.

From the proceedings of the scientific program of the Cutaneous Lymphoma Summit 2009, we have identified current limitations and needs in cutaneous lymphoma, basic and clinical science, and education. We summarize the priorities and potential opportunities for breakthrough advances. The following summary is intended to serve as a call to action for a strategic growth of multidisciplinary collaborations and resources, and to serve as a white paper by which we can measure our progress in future years.

Research Overview

From populations to genes, we have only a hint as to the origins of cutaneous lymphomas. It appears to be an acquired disease with a yet-to-be-identified etiology. Epidemiology studies providing an accurate disease frequency and prevalence are still lacking. Recent analysis of the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) Program demonstrated that reported CTCL incidence rates have been steadily increasing in the United States; yet, there was a significant degree of misclassification of cutaneous lymphomas within the SEER database. Accurate classification and epidemiology data collection are essential to the research effort, and its improvement in CTCL remains a priority.

Insights into the genetic susceptibility (disease-associated gene polymorphisms and/or germline mutations) of cutaneous lymphomas are limited. No significant non–Major Histocompatibility Complex associations were identified in genome-wide association studies of non-Hodgkin lymphoma or in the only study specific for CTCL. Limited observations of familial CTCL and linkage to HLA HLA-DRB1*11 and HLA-DQB1*03 have been reported, however, and these families provide a unique opportunity to further explore the genetic susceptibility of CTCL. The frequency of acquired somatic mutations, most commonly involving gains and losses in chromosomes 17, 10, 8, and 7, have been characterized, but no specific CTCL mutations have been identified with disease transformation or progression. Epigenetic changes in CTCL have only recently been investigated and suggest that alterations in methylation may influence resistance to Fas-mediated apoptosis observed in advanced-stage disease (SS). Greater molecular genetic studies are needed in cutaneous lymphomas.

Great advances have been made in the arena of immunobiology of CTCL. The malignant T-cell clone has been characterized in terms of its immunophenotype (skin-homing CD4 helper T cells) and cytokine profile (Th2). These insights into the immunopathogenesis of CTCL have provided the rationale for immunotherapies that have translated into novel therapies that have extended median survival in advanced stages. Further advances would be greatly accelerated by the greater availability of research reagents, such as stage-related cell lines, animal models, and tissue microarrays.

Clinical research in cutaneous lymphomas has historically been hampered by a limited capacity to recruit patients into clinical trials. Multi-institutional and multidisciplinary coordination of clinical trial initiatives is imperative and meant to overcome this obstacle to accelerate new drug approvals. The United States Cutaneous Lymphoma Consortium is a newly emerging multidisciplinary professional organization with the mission of developing a US-based clinical trial network comparable to the European Organization for Research and Treatment of Cancer CTCL trials platform. This will meet an important and currently unmet need.

As in all fields, recruitment of the best and brightest into the cutaneous lymphoma research arena ensures progress and advancement. The mentoring from established investigators of individuals early in their career development is an essential element of recruitment and retention. Joint multidisciplinary mentoring and educational programs would best serve basic and clinical investigators entering the field of cutaneous lymphomas.

A unique aspect of the research agenda of skin-based lymphomas is that it connects the worlds of dermatology and oncology. Traditionally, cancer research is funded by the National Institutes of Health (NIH) through the National Cancer Institute (NCI), and skin research is funded through the National Institutes of Arthritis, Musculoskeletal and Skin Diseases (NIAMS). There are aspects of the neoplastic nature of cutaneous lymphomas that affect non-neoplastic mechanisms in the skin, such as barrier function, pruritus, cutaneous immunology, microbiology, and photobiology. These dermatology-related aspects of cutaneous lymphoma are important and relevant in areas of skin research. Because they are associated with a cancer, however, cutaneous lymphoma grant applications are typically triaged to the NCI and compete against other cancer grants. A broader view regarding the eligibility of cutaneous lymphoma grant applications within and between the NCI and NIAMS would potentially increase the funding opportunities for cutaneous lymphoma investigators.

Research Needs and Opportunities

We have identified the following research needs and opportunities that would benefit the cutaneous lymphoma community:

1. Improve epidemiology resources and accuracy in data collection in population-based databases capturing CTCL cases, and define prevalence, mortality rate, co-morbidities and burden of disease of cutaneous lymphomas
2. Improve cutaneous lymphoma classification schemas by replacing the term mycosis fungoides with an appropriate lymphoma designation
3. Develop new laboratory reagents—cell lines, animal models, tissue microarrays—and platforms for access and sharing among investigators worldwide
4. Identify genetic markers in familial cases of CTCL
5. Identify immune correlates in patients who benefit from immunotherapies
6. Establish infrastructure to accelerate multicentered clinical trial design and implementation worldwide
7. Build a multidisciplinary mentoring program for young investigators in translational research
8. Increase recognition of the multidisciplinary nature of the cutaneous lymphoma research agenda with NIH policy makers

Clinical Care
Access to expertise and coordination of care are 2 of the most important priorities that patients with cutaneous lymphomas must address as they navigate through our complex health care system. A multidisciplinary approach to the diagnosis and treatment of cutaneous lymphomas brings together experienced pathologists, dermatologists, medical and radiation oncologists, nurses, and social workers. It maximizes the coordination of care and communication among providers and their patients. Greater access to these programs is needed.

When new drugs for cutaneous lymphomas are developed and approved by the US Federal Drug Administration, they are excluded from many drug formularies of health insurance carriers, enhancing their availability. There still remain active and effective therapies, however, that have not been formally approved for the indication of cutaneous lymphoma. As such, they are excluded from many drug formularies, and their exclusion produces great financial and logistical obstacles for many patients seeking these therapies. Current treatment guidelines for CTCL, updated each year by the National Comprehensive Cancer Network (NCCN) list multiple therapies for each disease stage. The NCCN treatment guidelines should serve as a resource for health care insurers, and listed CTCL treatments should be included in formularies as appropriate therapies. Evidenced-based treatments of choice, linked to response rates or survival endpoints, are not currently available within the NCCN CTCL guidelines. Development of an evidence-based treatment algorithm in CTCL would greatly enhance and standardize CTCL therapy.

Clinical Care Needs and Opportunities
We have identified the following clinical care needs and opportunities that would benefit the cutaneous lymphoma community:
1. Establish multidisciplinary care as the standard of care for cutaneous lymphomas
2. Include established treatments, within current guidelines, in all prescription drug formularies, and improve patient access to established treatments
3. Establish evidence-based treatment algorithms
4. Increase patient access to multidisciplinary treatment centers and support thorough Internet resources

Patient, Physician, and Nursing Education
Scientific advances and medical education in cutaneous lymphomas have traditionally been segregated into individual scientific societies and medical specialties with limited cross-talk through these traditional boundaries. Often, the flow of knowledge will span across multiple meetings that potentially duplicate educational efforts, overutilize limited resources, and increase the burden of participation for those in the field or those wishing to enter the field. One of the themes of the Cutaneous Lymphoma Summit 2009 was to create an all-inclusive forum, bringing together all stakeholders. We consider its format successful, and it should serve as a model for future coordination of multidisciplinary cutaneous lymphoma meetings.

As a result of the inclusion of members of the Dermatology Nursing Association (www.dnanurse.org) in the Cutaneous Lymphoma Summit 2009 program, the need of dermatology education in oncology nursing became apparent. With the high level of educational programs sponsored by the Dermatology Nursing Association, joint programming with oncology would enrich the care of patients with cutaneous lymphoma.

Throughout a patient’s journey, complex issues of diagnosis and management and their effect on quality of life arise. Most patients find that their time interacting with health care professionals does not meet all of their needs for information. The development of updated patient educational materials, and access to them, still remains an important need.

Patient, Physician, and Nursing Education: Needs and Opportunities
We have identified the following educational needs and opportunities that would benefit the cutaneous lymphoma community:
1. Establish an annual multidisciplinary professional meeting dedicated to cutaneous lymphomas and coordination of cutaneous lymphoma scientific meetings among professional societies and organizations
2. Establish a dermatology educational program for oncology nurses
3. Increase access of educational materials to patients

Summary
The inspirational tag line of the Cutaneous Lymphoma Summit 2009, “community, cooperation, cure,” brings into focus the great potential of future interdisciplinary efforts. Advances in communication technology have already provided a platform that has enhanced international collaborations. The call to action for greater achievements in cutaneous lymphomas requires that we take stock of our current status and identify strategic goals that can serve as benchmarks for our joint progress. The cutaneous lymphoma community would benefit from collaboration between all stakeholders—scientists, physicians, nurses, social workers, and patients—in developing coordinated strategies to address the needs and opportunities outlined above.

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References


Outsmarting Cutaneous T-Cell Lymphoma Cells by Decoding the Language They Speak: Focusing Past and Present Insights on Future Prospects

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Keywords: CTCL, Dendritic antigen cells, Leukapheresis

Early History of Cutaneous T-Cell Lymphoma

After the term “cutaneous T-cell lymphoma” (CTCL) was introduced in 1974, investigation of the biology of the malignant T cells has contributed heavily to an understanding of the clinically important biology of benign and neoplastic T cells. The availability of large numbers of clonal skin-homing CTCL cells facilitated the discovery of T-cell–specific monoclonal antibodies (MoAbs) and identification of helper T cells. Tight linkage between the biology and clinical manifestations of CTCL cells has enabled major and accelerating scientific and practical advances. Cutaneous T-cell lymphoma cells are now well defined by their distinctive features: membrane molecules that direct them to the skin; growth dependency on signaling from immature dendritic antigen-presenting cells; origin from the large set of normal “cutaneous T-cells” that recirculate between skin and blood; differentiation markers that control the way they interact with antigen-presenting cells, maintain memory for their cognate antigen, and regulate normal T cells; and clinical manifestations of CTCL cells to develop better therapies? Can we ultimately outsmart CTCL cells by interrupting their capacity to receive the growth stimulatory signals that they require to grow and spread? The term “cutaneous T-cell lymphoma” was introduced in 1974 at a special clinical staff conference at the National Institutes of Health (NIH) and published in full the following year in the Annals of Internal Medicine. As this Summit strives to identify important future directions for research into the pathogenesis, diagnosis, and treatment of those lymphomas that present through the skin, an assessment of how far we have come since that time provides helpful context and perspective. Because I participated in the CTCL naming ceremony, and hope to continue contributing to the malignancy’s defeat, the organizers of the Summit have kindly asked me to frame the subject.

Of all the cancers being investigated at the NIH in the mid-1970s, the reason that CTCL was chosen as the focus of that conference was the excitement that its conception had generated. Human T-cell lymphoma had burst onto the scene precisely at that time, enabling the unifying discovery that those lymphomas presenting through skin infiltration were common cancers of T cells, regardless of the descriptive names attached to them (mycosis fungoides [MF], Sézary syndrome [SS], reticulum cell sarcoma, lymphoma cutis, follicular mucinosis, etc). In stark contrast, those lymphocytic malignancies that were found in adults in the absence of skin infiltration were most commonly of B-cell origin. The effect of this dichotomy was enhanced by the clinical observation, in those days before the magic of chemotherapy was subdued by the realization of its toxicity and limitations, that intense pharmacologic therapy could convert MF and other skin lymphomas into SS or vice versa.

Because leukapheresis was palliative for the leukemic phase of CTCL, enormous numbers of malignant T cells were being removed from patients with a high count. The clonal nature of these cells made them exceptionally attractive research objects to virtually all NIH laboratories getting in on the ground floor of T-cell biology. In just over 3 years, a huge amount of scientific information, from all available immunologic angles, became available to integrate with the burgeoning clinical recognition that the
Decoding CTCL: Focusing Insights on Future Prospects

Abbreviation: CTCL = cutaneous T-cell lymphoma

majority of those lymphomas presented through skin infiltration, overlapped clinically and biologically. An invigorating view became prevalent: CTCL had become the first prominent example of the tight linkage between immunobiology and lymphoma manifestations, and diagnosis and therapy.

It was from those breakthrough insights that the concept of CTCL emerged. Up until 1974, MF and SS had been considered pre-malignant disorders that could develop into Hodgkin disease, lymphocytic leukemia, or other established lymphocytic malignancies. Recognition that MF and SS are clonal malignancies that share a distinctive histopathology and cellular features, and that they overlap clinically, led us to the conclusion that old misconceptions needed to be replaced by a new unifying nomenclature. Therefore, the term “cutaneous T-cell lymphoma” was introduced to allow patients to know that they had a genuine malignancy, requiring the best available therapy. Bringing these skin-homing lymphomas under a single nomenclature also empowered cancer biologists to search for common biologic properties of the malignant cells.

In the time frames between the first application of T-cell science, to the analysis of skin-homing malignant T cells, to the introduction of the term “CTCL,” several translational and clinically relevant insights accrued. Cutaneous T-cell lymphoma cells not only revealed to be malignant polyclonal helper T cells, they also provided the first demonstration that human T cells can support normal B-cell maturation. The specific accumulation of CTCL cells to those regions of the lymph nodes and spleen where normal CD4+ T cells localize, and their avoidance of bone marrow even under circumstances of extreme lymphocytosis, suggested that their distinguishing skin homing must reflect their generation from a subpopulation of normal cutaneous T cells. The immunosuppression that accompanied large tumor burdens of CTCL cells indicated that the malignant cells directly suppress normal immunologic function. A fast forward to current scientific understanding in the next section reveals how prescient those collective early insights and suggestions were (Figures 1 and 2).

**Common Scientific Denominators**

Scientific advances made over the intervening years have markedly clarified the biologic boundaries of CTCL. Yet, the path to the present has been a 2-way street as CTCL cells, as a source of clonally derived T cells, have contributed immensely to the maturation of human immunobiology in ways that have further improved our understanding of CTCL. For example, finding that anti-CD4 MoAbs bind to CTCL cells and that anti-CD8 MoAbs do not reveal CD4 as a marker of helper-inducer T cells, and CD8 as a marker of cytotoxic T cells.

Table 1 highlights 10 particularly important distinguishing CTCL features and their biologic importance. Topping the list is the recognition that CTCL is a malignancy of CD4+ skin-homing T cells, whose clinical manifestations in the skin reflect subclone evolution toward populations that progressively lose their growth dependency on the epidermal environment. From the vantage point of physician-patient communication, it is particularly important that patients hear and understand the word “lymphoma” in the title of their disease, so that they do not underestimate the benefits of successful early therapeutic intervention, and recognize that what they have is far more than a simple rash. The effectiveness of that communication has enabled simple skin-directed treatments, such as ultraviolet (UV) light exposure, to dramatically interrupt the natural progression of the malignancy and make CTCL one of the great stories of modern medicine.

The predilection of CTCL cells to localize in the epidermis and to accumulate in the pathognomonic Pautrier’s microabscesses is at the core of the disease’s pathogenesis. Because these collections are almost exclusively composed of malignant T cells and Langerhans cells (the dendritic antigen-presenting cells [DCs] of the epidermis), they form an exclusive club that likely offers a principal clue about the etiology of the lymphoma. The mandatory colocalization of these 2 cell types, along with the recognition that the epidermis is the early main site of CTCL proliferation, makes the CTCL cells highly vulnerable to skin-localized treatments for scientific reasons that will be discussed in the next section.

The discovery of cutaneous lymphoid antigen (CLA) as both a marker of the large T-cell subset (10%-15% of circulating T cells), now conveniently labeled “cutaneous T cells,” has been pivotal in our understanding of CTCL’s origin, manifestations, and biology. Elegant studies have revealed that CLA is a glycoprotein whose expression is triggered by the conversion of naive T cells into...
memory T cells, after exposure to skin-derived cognate antigens in lymph nodes that drain skin.15,16 Through adherence of circulating T-cell CLA to capillary E-selectin, which is upregulated on papillary dermal endothelial cells in skin sites of inflammation, cutaneous T cells are directed back to skin.

These discoveries provide extraordinary insights into the biology of CTCL. In the same way that melanoma is a malignant transformation of normal melanocytes, CTCL almost certainly derives from normal counterparts, the cutaneous T cells. Normally, CLA helps direct CTCL cells back to skin where, as in neoplastic amplification, they accumulate in the CTCL skin lesions. The exclusion of often dermatally abnormal normal reactive T cells from the CTCL cell–Langerhans cell liaison in lesional epidermis suggests that an additional factor preferentially attracts CTCL cells to the epidermis. Because CTCL cells differ from other memory CLA+ T cells in the specificity of the clonal T-cell receptor for cognate antigen, a strong candidate for the selective attractant of CTCL cells to the epidermis is, as of yet, the unidentified skin-localized antigen that originally converted their normal predecessors to memory T cell status. Therefore, I suggest that a key missing link to the pathogenesis of CTCL skin lesions, and even possibly to the malignancy’s origin, is the identification of the original antigen. The tendency of CTCL skin lesions to occur in sun-shielded areas, and then to return in precisely the same locations and even with same lesion configuration, implies a role for a persistent local influence, quite possibly the original antigen, that may be altered by large doses of sunlight.

The patch and early plaque stages of CTCL lesions commonly contain remarkably few epidermically concentrated CTCL cells, which elicit a marked dermal inflammatory infiltrate.17 This finding reveals that the clinically evident erythema actually represents the host response, rather than the malignant cells themselves. Hence, caution must be exercised in considering loss of erythema as a genuine clinical response.

**Tale of Two Cells**

In general, the tight relationship between Langerhans and CTCL cells extends to dendritic antigen cells (DCs). Initially, our group demonstrated that CTCL infiltrates to regularly include evenly dispersed DCs, most clearly demonstrated in cutaneous tumors.18 This phenomenon is such a regular feature of CTCL that the abundant presence of DCs is a useful means of microscopically distinguishing cutaneous B-cell lymphoma infiltrates from those of CTCL.

This finding, along with the composition of Pautrier’s microabscesses, suggested to us that DCs provide in vivo growth signals to CTCL cells. Although it has long been known that CTCL cells are difficult to propagate in tissue culture, we found that cocultivation of CTCL cells with autologous immature DCs facilitated marked CTCL cell replication.19 This nurturing effect required that the DCs be kept immature, by the addition of IL-10. If the DCs were permitted to mature, the cultured CTCL cells died.

This system permitted us to establish that the DC-CTCL interaction was mediated by the engagement of the CTCL T-cell receptor by the class II major histocompatibility complex of the cultured DC. The DC that was present processed antigen to CD4 T cells through precisely that type of cell-to-cell contact. Hence, the possibility must be considered that CTCL cells may be stimulated to proliferate by DCs through an interaction reminiscent of classic antigen presentation. Because the culture system used does not provide access to antigen derived from lesional skin, if antigen participates in this phenomenon, it must be either a self antigen or one associated with the CTCL cells themselves.

Although fundamental aspects of the DC-CTCL interaction remain to be determined, it is clear that CTCL cells have a rigid in vitro requirement for the nurturing effects of DCs. The probability that this requirement exists in vivo as well raises the intriguing possibility that the exquisite sensitivity of CTCL plaques to UV therapy may result from the known sensitivity of DCs to both UVB- and UVA-activated psoralens in PUVA therapy. This observation provides an attractive potential explanation as to why ultraviolet therapy, administered as infrequently as in 3-month intervals, can maintain CTCL remissions. Dendritic antigen cells that are periodically depleted by such therapy must be repopulated over months. Therefore, periodic depletion of epidermal DCs likely interrupts the growth signaling.

Further studies of the interplay between DCs and CTCL cells should provide answers to these questions. The early intervention in CTCL lesions that has become standard care is the most logical explanation about why the prognosis of the malignancy has been so enormously improved over the past 2 decades. This clinical success ranks as one of the most impressive advances in the clinical care of serious cancers, and offers hope that, with continued deciphering of CTCL growth requirements, malignant cell vulnerabilities can be exploited even further.

**Future Prospects**

Although major questions remain about the etiology and pathogenesis of CTCL, enormous progress has been made on these
Decoding CTCL: Focusing Insights on Future Prospects

fronts over the past 3 decades, since it was first recognized as a broad entity. Many CTCL clinicians have long suspected that the malignancy is far more common than indicated by national registry data, and recent information has revealed that it is at least 8 times as common as previously known. More homogeneity of nomenclature and improved registering of cases will probably increase that estimated incidence further.

With the number of strong research groups studying the biology of CTCL increasing, application of technical advances in molecular immunology and genetics should accelerate our decoding of the language that CTCL cells speak. Personally, I am very optimistic that the next decade will give us the tools to treat the advanced stages of CTCL as safely and effectively as possible for the early stages.

Disclosures

Richard L. Edelson is an employee of the Yale School of Medicine. He is the president of the Dermatology Foundation. He has received research support from the National Cancer Institute.

References

Introduction

Cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma (CBCL) have garnered tremendous interest among the basic science and epidemiologic communities. The potential viral, biochemical, or genetic origins of these cancers remain to be fully defined. Additionally, the reported incidence of these cancers has risen sharply over the past 15 years, which may be due to a combination of real increases in cases and improved access to and detection by medical practitioners.

The primary source for analyses of incidence in the United States is the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI). The SEER program collects data on cancer incidence, mortality, and survival at the population level, now covering approximately 26% of the US population. Data are derived primarily from hospitals, larger practices and health systems, and pathology laboratories.

Incidence Trends

Cutaneous T-Cell Lymphoma

Reported incidence rates have been steadily increasing for CTCLs in the United States from 1973 to 2002 (Figure 1).1 Overall, CTCL incidence rate in 1998-2002 was 9.6 per million person-years, a major increase from 2.8 per million person-years in 1973-1977. Mycosis fungoides (MF) has continued to be the predominant CTCL type from 1973 to 2002; it represents 72% of CTCL cases.

Additionally, incidence rate rises with increasing age. It is quite low before the age of 20 years (0.3 per million person-years) and peaks in the 70-79-year age group (24.6 per million person-years; Figure 2).1 Men have higher CTCL incidence rates than women (Figure 3). Male-female incidence rate ratios (IRRs) have declined from 2.5 in 1973-1982 to 1.7 in 1993-2002, suggesting a trend over these decades toward increasingly similar male and female incidence rates (Figure 4). Male-female IRRs are substantially greater at older ages than among younger adults (Figure 5). Middle- and older-aged adults have had decreasing male-female IRRs from 1973 to 2006 (Figure 6).

Cutaneous T-cell lymphoma has notable racial and ethnic incidence differences, with much higher rates among blacks than among whites (Figure 3).1 Black-white IRRs decrease with advancing patient age, hence older blacks have rates of CTCL that are more similar to those of whites than one finds at younger ages (Figure 5). The black-white IRR declined over recent decades from 1.8 in 1973-1982 to 1.3 in 1993-2002 (Figure 4). The Hispanic white group and Asian/Pacific Islander group had the same incidence rates of CTCLs (5.1 per million person-years), significantly
lower than incidence rates for the black group (10.0 per million person-years) and white group (8.1 per million person-years) for the same years. Black-to-white and male-to-female ratios both have decreased over time, but, as described above, they have opposing trends with age.

Cutaneous T-cell lymphoma incidence rates have been noted to vary substantially with geographic location within the United States. San Francisco, Detroit, Connecticut, and Seattle were noted to have the highest reported rates (in decreasing order). Although whites had a lower incidence rate than blacks in Los Angeles, Atlanta, Detroit, Seattle, and Connecticut from 1993 to 2002, blacks experienced the lower CTCL incidence rate in San Francisco (Figure 7). Incidence rates among the different SEER registries have been associated with increasing physician density and medical specialist density, high median family income, higher proportion of adults with a bachelor’s degree, and with a high median value of owner-occupied housing units. All of these are indicators of higher socioeconomic status, which might suggest the possibility that these trends could be due to better CTCL detection.

Cutaneous B-Cell Lymphoma

The overall CBCL incidence rate in 2001-2005 was 3.1 per million person-years, less than half that of the CTCL. Of mature B-cell neoplasms, the most common were cutaneous diffuse large B-cell lymphoma, cutaneous follicular center lymphoma, and cutaneous marginal zone B-cell lymphoma (40.1%, 30.0%, and 24.8% of CBCL, respectively; Figure 8). The incidence rate of CBCLs is nearly double in men (4.0 per million person-years) as compared with women (2.3 per million person-years; Figure 9). Cutaneous B-cell and T-cell lymphomas differed in distribution among racial and ethnic groups (Figure 10); CBCLs were more commonly found in non-Hispanic whites (3.5 per million person-years), than in blacks (1.5 per million person-years). This is the opposite of the gradient observed in CTCL, which underscores the importance of distinguishing between these diagnostic groups in investigating these disorders.

Norway and France have lower incidence rates of CTCLs than the United States. Both countries showed a sharp increase in CTCL incidence rates between 1990 and 2003 (Figures 11 and 12). France was found to have a significantly greater CTCL incidence rate than that of Norway (5.7 per million person-years vs. 2.9 per million person-years).
person-years) particularly in the last years of the study (1995-2003). Males had higher rates of CTCL than women in Norway, of CBCL in Italy, and of overall primary cutaneous lymphoma in France (Figure 13). Mycosis fungoides was the predominant form of CTCL in the United States, France, and Norway. Primary cutaneous follicular center lymphoma was the most common type of CBCL reported in France (46%) and Italy (57%; Figure 14), but was only 30% of CBCL in the United States (Figure 8).

Limitations and Strengths

The SEER program’s strengths lie in the quality control within the federally funded program, and its population-based data set. There are several limitations to the data that has been collected by SEER and other registries. The most important limitation of incidence data are the accuracy of the diagnosis in the populations they cover. Cutaneous lymphomas, in their early stages, often mimic atopic and contact dermatitis leading to clinical misdiagnosis; histologic misdiagnosis may also be frequent. Additionally, inaccuracies may be decreasing over time because of a rise in the number of dermatologists in the United States. The increase in diagnoses in recent years might be associated with earlier detection of CTCLs or a rise in misdiagnosis of benign dermatoses. Lack of independent verification of diagnoses underscores the importance of accuracy in diagnosis. Under registration in the US might occur when the diagnosis is not made within a registry area or is not associated with a pathology report from a laboratory that reports to the registry. The SEER program’s under registration has been estimated in 1 study, in which 17% (8 out of 47) of MF cases were not enrolled in the SEER registry. Limited funding in registries may lead to failure to keep up with our changing healthcare system and therefore contribute to errors in SEER data. Changes in ICD-O coding used by SEER resulted in 4% of total cases histologically classified as CTCL, but erroneously noted as having B-cell lineage. Furthermore, the changing codes might play a role in apparent CTCL cell type redistributions. Reporting delay of the most recently diagnosed cases may distort incidence rates in recent years. Although SEER allows about 2 years to report the recently diagnosed cases, allowing for 88%-97% of cases to be collected; 1 study suggested that 4-17 years would be required in order for 99% of cases to be reported. Another study suggested that, between 1990 and 1994, incidence rates of MF and Sézary syndrome were underestimated by 6% in SEER because of delayed reporting.
Mortality Trends

Inaccuracies in mortality rates stem from errors in death certification and disease classification. Only 60% of deaths attributed to MF and only 44% of deaths from CTCL were certified as such, whereas 93% of deaths attributed to melanoma were certified as a result of melanoma. Certification of cutaneous lymphoma deaths as being due to lymphoma not otherwise specified might also account for the substantial undercertification of this cancer. Because of the reliance on death certification, mortality data may not be entirely reliable for cutaneous lymphoma.

Analytical Epidemiology

Several case-control studies have explored risk factors for MF. One study documented a dose-response association of alcohol consumption with increased risk of MF. Furthermore, the risk for MF was significantly increased with combined exposure to both smoking and alcohol use. In a multicenter case-control study, Morales-Suarez-Varela examined other potential risk factors for the development of MF. Occupational exposures in pottery, glass, and ceramics industries (odds ratio [OR], 17.9; 95% CI, 5.4–59.4) and with pulp and paper product manufacturers (OR, 14.4; 95% CI, 2.2–95.1) had the highest risk for MF. Morales et al also examined potential viral and atopic risk factors: patients with psoriasis had the highest risk of developing MF (OR, 7.2; 95% CI, 3.6–14.5). These studies suggest that while lifestyle, occupational, and genetic factors may be risks for MF, confirmatory studies are needed, and there are other factors that might play a significant role in the development of MF. This case control study was large and cases were recruited from several European countries; however, response rates were low.

A US case control study suggested that MF risk was associated with past history of malignancies and increased tendency to sunburn. A later study failed to find that a significant MF risk exists in patients with a history of cancer. Another study rejected occupational, social, environmental exposures, and personal history of atopic dermatitis as risk factors for MF. However, this same study did find that family history of atopic dermatitis had a significant association with MF. A more recent study reaffirmed the current lack of causal relationship between atopy and CTCL. While case control studies allow researchers to overcome limitations because of the low incidence of cutaneous lymphomas, these studies are weakened by potential inaccurate reporting of risk factors and selection biases of both cases and controls.

Conclusion

Cutaneous lymphomas exhibit wide variation in their frequency by cell type, among races, between sexes, and geographically. There is much opportunity for better understanding, prevention, and treatment of this disease. Increased accuracy of diagnosis will better address potential underreporting of cutaneous lymphoma subtypes in the SEER database.

Disclosures

The authors have no relevant relationships to disclose.

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Familial Mycosis Fungoides: Model of Genetic Susceptibility

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Introduction
The familial occurrence of mycosis fungoides (MF) is regarded as a rare event, with reports of only 15 families, each composed of 2 first-degree relatives with the disease. According to the available data, it seems that familial MF does not differ from sporadic MF in terms of phenotype and clinical outcome. The familial clustering of MF, together with the detection of certain human leukocyte antigen (HLA) class II alleles with this malignancy (sporadic and familial), suggest that genetic factors might play a role in MF. With the increasing evidence supporting the importance of genetic determinants in lymphomagenesis, further attempts with international collaboration should be made to elucidate the possible genetic basis of the familial clustering of MF. Such consortial efforts will enable others to better define the epidemiology and phenotype of familial cases and, with the use of advanced molecular approaches, enhance our ability to identify susceptibility genes involved in familial MF.

Mycosis fungoides is the most common cutaneous lymphoma, characterized by a CD4+ clonal expansion in the skin, admixed with a reactive lymphocytic infiltrate composed largely of CD4+ cells. The etiopathogenesis is still unknown; however, researchers suggest that it arises from a state of persistent antigenic cell stimulation1 to infectious agents, chemical agents, or other environmental factors. The majority of MF cases are diagnosed with no discernible family history of cancer and specifically of MF. Familial clustering of MF is regarded as a rare occurrence that could be explained by a common exposure to a causal agent, a genetic predisposition, or both.

By contrast to MF, familial clustering of non-Hodgkin lymphoma,2 Hodgkin lymphoma,3 and chronic lymphocytic leukemia (CLL)4 is well established. These observations, together with the coaggregation of different chronic lymphoproliferative neoplasms in the same family reported on large-scale studies, support a genetic role in such high-risk families.5,6

The aim of the this report is to present the sparse literature on the epidemiology and phenotype of familial MF, review the limited genetic studies performed on familial MF, and discuss possible future clinical and genetic studies.

Epidemiology and Phenotype of Familial Mycosis Fungoides
Until the early 2000s, the occurrence of MF in relatives was regarded as an extremely rare event, with reports of only 8 such families from different parts of the world. Each report included an index patient from a single family in which another first-degree relative was also affected. Five families were from the United States,7,11 and 1 each were from Israel,12 Iraq,13 and Turkey.14 Four families had a parent-child pair,7,9,10,14 and 4 had sibling pairs,8,11-13 including 2 in which the siblings were monozygotic twins.11,13

Prompted by these previous publications, in 2001, we reviewed the files of 300 patients with MF who attended 2 departments of dermatology in Israel in 1991-2001 for familial occurrence. The relevant patients were identified, and their first-degree relatives underwent a dermatologic examination. A total of 6 families, each with 2 first-degree relatives with MF, were detected.15 In 5 families, 2 members had MF, and in 1 family, 1 member had MF and 1 had large plaque parapsoriasis, regarded by many authors as the earliest stage of MF.16 In 1 family, there was a history of leukemia in an additional first-degree relative, suggesting that MF might sometimes be part of familial predisposition to hematologic malignancies, as previously described.9 In 5 families, there were 2 affected siblings; the sixth family had a parent-child pair. All families were of Jewish ancestry, with no history of consanguineous marriages. There was a male predominance (2:1), as in sporadic MF. In 5 families, the affected patients were adults with a similar mean age of onset and diagnosis (45.8 and 48.5 years, respectively) to patients with sporadic MF attending 1 of the institutions participating in the study (45 and 52 years, respectively). In the remaining family, both siblings were children at the time of diagnosis. Interestingly, there is only 1 subsequent report in the literature on juvenile MF.
familial MF, published by an Italian group. Thus, the percentage of juvenile cases of familial MF (4 of total 30 cases reported in the literature) does not differ significantly from that found in our cohort of sporadic MF (unpublished data). All of our 12 patients had early-stage disease, and similar to sporadic MF showed good response to skin-targeted therapy.

This preliminary study led to 2 conclusions. First, the familial aggregation of MF among Jewish patients in Israel is not as rare as reflected in the literature. Several explanations may account for this observation. It might reflect an inherited predisposition specifically prevalent among the Jewish population, similar to the high rate of mutations in other cancer predisposition genes (e.g., BRCA1, BRCA2). Alternatively, it might be a consequence of a lack of high index of clinician awareness combined with the easy access to medical services and close familial ties (with a free flow of medical information among family members) characteristic of our tiny country. The second tentative conclusion is that familial MF does not seem to differ from sporadic MF in terms of phenotype and clinical outcome. Similarly, in CLL that has the strongest familial tendencies of all hematologic malignancies, there do not appear to be striking differences between familial and sporadic cases.

The Search for a Genetic Basis of Mycosis Fungoides: Studies of the Human Leukocyte Antigen System

Given the limited number of families with MF, a comprehensive assessment of the genetic basis of this seemingly inherited predisposition was impossible. One way of gaining insight into the putative genetic basis is the candidate gene approach. The most likely candidate genes are those involved in the HLA system. The candidacy of this system stems from the results of a few previous studies reporting on the association of certain HLA class II alleles and sporadic MF, and previous studies on the involvement of this system in the pathogenesis of other lymphoproliferative disorders.

The HLA system, also known as the human histocompatibility complex, is intimately involved in immune responsiveness, as these cell surface molecules present antigenic peptides to the immune system for recognition of self and non-self. The HLA region, located on the short arm of chromosome 6, has already been mapped. Approximately 220 genes have been defined. Many of these genes encode not only for the surface proteins that present antigenic peptides to the immune system, but also proteins involved in immune and inflammatory responses, such as tumor necrosis factor superfamily and heat shock proteins.

Since MF was suggested to arise from a state of chronic antigenic stimulation, as early as 1983, Safai et al. studied the role of the HLA in the pathogenesis of sporadic MF. Using the traditional cytotoxicity test, a significant increase in the frequency of DRB1*11 (formerly termed “DR5”) was found in a group of Caucasian patients from North America. Later, Jackow et al. applied more accurate and specific DNA-based molecular typing, which allows for a higher definition of HLA, confirming the association of DRB1*11 with MF in another group of North American Caucasian patients. In addition, our group observed similar findings in Ashkenazi Jewish patients from Israel.

Furthermore, significantly high incidence of BQB1*03 alleles was found in the group of Caucasian patients from North America, and in both Ashkenazi and non-Ashkenazi Jewish patients with MF. Support for the role of certain class II alleles in the development of lymphoid neoplasms was also provided by association studies in Hodgkin lymphoma and CLL. Interestingly, a recent study showed an increased frequency of HLA-DQB1*03 alleles in the Korean population with non-Hodgkin lymphoma (B- and T-cell disease). The importance of the HLA locus in the pathogenesis of lymphoproliferative malignancies has further been reported by a recent genome-wide association study; genetic variants at chromosome 6p21.33 in the Major Histocompatibility Complex were found to be associated with susceptibility to follicular lymphoma. In another study using high-density single-nucleotide polymorphism (SNP) genome-wide linkage analysis that genotyped 206 families with familial CLL, 3 top predisposing loci were identified, and among them, an SNP located to chromosomal position 6p21 was found.

We investigated the HLA system in our 12 patients with familial MF and their first-degree relatives. We were unable to identify a specific HLA-DR allele that was overrepresented. However, the DQB1*03 allele was found to be significantly increased compared with the normal control group.

Our cases of familial clustering of MF, together with those reported by others, and the detection of DQB1*03 alleles in association with sporadic and familial cases, suggest that genetic factors might play a role in the development of and/or the susceptibility to MF.
Future Directions in the Study of Familial Mycosis Fungoides

Given the rarity of MF in general, and familial cases in particular, it is obvious that any further attempts to elucidate the genetic basis of inherited predisposition or familial clustering require an international collaboration and worldwide registry. Such consortial efforts will facilitate better definitions of the rate of familial occurrence and help shed light on the clinical, pathologic, and other biologically relevant features of familial MF. In addition, applying advanced molecular biologic techniques (eg, selectively massively parallel DNA sequencing [next-generation sequencing] of complete coding regions [whole exome])\textsuperscript{29,30} will enhance our ability to identify susceptibility genes (and the mutations they harbor) involved in the familial MF.

Disclosures

The authors have no relevant relationships to report.

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What Can Psoriasis Teach Us About the Genetic Basis of Cutaneous T-Cell Lymphoma?

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Introduction
Psoriasis is a germ-line polygenic disorder in which major histocompatibility complex class I appears to play a major role, whereas cutaneous T-cell lymphoma (CTCL) is likely influenced by germ-line variation but appears to be driven largely by somatic mutations; although familial cases of CTCL have been identified, the rarity of the disorder makes it difficult to apply the large case-control sampling strategy that has led recently to the identification of multiple susceptibility loci in psoriasis and other immune-mediated disorders. While underlying genetic variation may play a role in contributing to the spectrum of phenotypic variation in CTCL, current knowledge suggests that this disease is best understood in terms of somatic mutations occurring in pathogenic T-cell clones, resulting in a further host immune response. Whether germ-line or somatic, alterations in various components of nuclear factor-κB signaling may prove to be an important final common pathway in both disorders.

Cutaneous T-cell lymphoma is a heterogeneous group of extranodal non-Hodgkin lymphomas (NHLs) targeted to the skin,¹ with mycosis fungoides (MF) and Sézary syndrome (SS) being most familiar to dermatologists. Mycosis fungoides and psoriasis are both mediated by skin-homing T cells. While the 2 disorders are readily distinguished histologically, they can occasionally be confused clinically, leading to worsening of MF after anti–tumor necrosis factor (TNF) treatment.² In both disorders, there is clonal expansion of skin-homing memory T cells and a milieu that encourages polyclonal T-cell activation.³ However, there are important differences. In psoriasis, expansion of pathogenic T cells tends to be oligoclonal and may be due to chronic antigen stimulation originating in the tonsils,⁴ whereas in MF, clonal expansion is accompanied by genomic instability affecting genes involved in cell survival and apoptosis.⁵ Furthermore, in CTCL there is a nonclonal population of cytotoxic CD8+ T cells and possibly natural killer cells that is thought to be involved in controlling the malignant T-cell clone,⁶ whereas most pathogenic schema for psoriasis lack such a population. Moreover, in MF, CD8+ T cells are found in both the dermis and epidermis, where as in psoriasis, they are largely confined to the epidermis.³

The potential importance of antigenic stimulation in maintaining the malignant clone in MF has been emphasized⁷ but remains incompletely understood. While the classic Pautrier microabscesses indeed represents a clustering of epidermal T cells around epidermal Langerhans cells, these are immature antigen-presenting cells with strong phagocytic function but weak major histocompatibility complex (MHC) class II expression and stimulatory activity. Suggestive of a role for antigen-dependent MHC–T-cell receptor (TCR) engagement, MF is an HLA-associated disorder, and immature antigen-presenting cells derived from extracorporeal photopheresis support long-term proliferation and survival of CTCL cells in a contact- and TCR-dependent manner.⁸ However, most studies have not directly addressed the role of MHC class II in supporting proliferation or blocking apoptosis through the use of class II–blocking antibodies. Indeed, there is recent evidence that reduced signaling through the TCR is important for CTCL cell survival.⁹

Psoriasis and CTCL also manifest prominent differences in the cytokine milieu, with psoriasis being dominated by a mixture of Th1, Th17, and Th22 cells,¹⁰¹¹ whereas MF is Th2 dominant,⁶ as is atopic dermatitis.¹² Correspondingly, the innate immune response of the epidermis in psoriasis features much higher expression of the interleukin (IL)-17 target gene DEF4 (encoding human β-defensin-2) than does either atopic dermatitis or MF.¹³¹⁴

In this article, we will explore the role of genetics as a tool to better understand the pathogenesis of MF and SS. After briefly reviewing the genetic epidemiology of MF (see also an article by Hodak on familial MF in this issue), we will focus on psoriasis as a prototypical polygenic immune-mediated disorder, contrast the germ-line genetics of psoriasis to the prominently somatic cell genetics of MF, and consider how recent discoveries in psoriasis genetics might serve to define pathways relevant to both disorders.

Genetic Epidemiology of Cutaneous T-Cell Lymphoma
Cutaneous T-cell lymphoma is a rare disorder. Two studies have placed the incidence rate of CTCL in the United States at approxi-
mately 8 new cases per 1,000,000 person-years.\textsuperscript{15,16} By contrast, the incidence of MF in Rochester, MN, has been estimated at 600 new cases per 1,000,000 person-years,\textsuperscript{17} nearly 100 times higher. The low incidence of MF makes it difficult to carry out well-powered studies of its genetic epidemiology, and as a result, available data for MF are very sparse. Two recent studies have estimated the overall recurrence risk for NHL to be significantly elevated in first-degree relatives of patients with NHL, with a standardized incidence ratio of 1.8 (95% CI, 1.4–2.2) for parents and 1.9 (95% CI, 1.3–3.2) for siblings in 1 study,\textsuperscript{18} and an odds ratio (OR) of 1.4 (95% CI, 1.0–1.8) for parents and 2.0 (95% CI, 1.4–2.8) for siblings in the other.\textsuperscript{19} By contrast, recurrence risk estimates for first-degree relatives of psoriasis patients range from approximately 4 to 8\textsuperscript{20} and as high as 35 for psoriatic arthritis.\textsuperscript{21} While none of these measures is precisely mathematically equivalent, it is clear that the familial tendency to develop psoriasis is clearly greater than it is for NHL. Thus, psoriasis is not only more prevalent, but it also displays much stronger familial aggregation.

Despite these challenges, there is evidence for the importance of germ-line genetic variation in CTCL. There is long-standing serologic evidence that MF is associated with HLA-DR5,\textsuperscript{22} with later DNA-based refinement to HLA-DRB*11 and HLA-DQB1*03.23-25 Interested readers are referred to the article by Hodak elsewhere in this issue for additional details. More recently, there have been several studies on non-MHC genetic polymorphisms in NHL,\textsuperscript{26-35} but only 1 focused exclusively on MF.\textsuperscript{36} All but 1 of these have been candidate gene studies, focusing on hormone-metabolizing genes,\textsuperscript{37} folate-metabolizing enzymes,\textsuperscript{38} oxidative stress–related genes,\textsuperscript{39} cytokine and cytokine receptor genes,\textsuperscript{40,33,35,36} and innate immunity genes.\textsuperscript{27} Interestingly, this signal mapped to a region of strong linkage disequilibrium containing the STG gene, which extends to HLA-Cw6 and largely defines our current understanding of the PSORS1 (psoriasis susceptibility 1) mapping interval. This interesting finding will be discussed later in more detail. Likely because of limited sample size, no significant non-MHC associations were identified in the NHL GWAS\textsuperscript{31} or in the only study specific for CTCL.\textsuperscript{36} However, there is 1 report of increased risk for MF in carriers of a lymphotoxin gene variant in the MHC class I region.\textsuperscript{31} Interestingly, this signal mapped to a region of strong linkage disequilibrium containing the STG gene, which extends to HLA-Cw6 and largely defines our current understanding of the PSORS1 (psoriasis susceptibility 1) mapping interval. This interesting finding will be discussed later in more detail. Likely because of limited sample size, no significant non-MHC associations were identified in the NHL GWAS\textsuperscript{31} or in the only study specific for CTCL.\textsuperscript{36} However, there is 1 report of increased risk for MF in carriers of a lymphotoxin gene variant in the MHC class I region (LTA 252G; OR, 1.44; \(P = .015\)).\textsuperscript{35}

On the other hand, a wealth of recent information emphasizes the importance of genomic instability and somatic mutation in CTCL, with complex patterns of segmental gains and losses and/or uniparental disomy on chromosomes 1, 4, 8, 10, 17, 18, and 19.\textsuperscript{5,38-41} Interestingly, there are pronounced gene amplifications and/or alterations of mRNA expression for several genes mapping to these chromosomal regions.\textsuperscript{5,15,42,43} Thus, as would be expected for a cancer that typically appears late in life, somatic mutation and genomic stability probably play a more obvious role in CTCL than does germ-line variation, although germ-line variation is a likely contributor to disease risk and outcome. We will return to these studies after considering recent advances in the genetics of psoriasis.

**Genetics of Psoriasis**

Many genetic epidemiology studies have found that psoriasis is multifactorial, meaning that both genes and environment contribute to the risk of disease.\textsuperscript{20,44} Psoriasis has long been known to be HLA associated, with early studies mapping the determinant to the MHC class I region.\textsuperscript{45} Psoriasis vulgaris is strongly associated with HLA-Cw6, and these associations are strongest in patients manifesting early onset, guttate psoriasis, positive family history, and more severe disease. The same associations have been observed in white\textsuperscript{46} and Han Chinese populations.\textsuperscript{47} In 2006, we reported that HLA-Cw6 was the likely cause of these HLA associations in psoriasis,\textsuperscript{48} and this was also confirmed in the Han Chinese.\textsuperscript{49}

In the 1990s, genetic studies of psoriasis were largely conducted on families, using the technique of genetic linkage to provide an unbiased search of the genome using a few hundred microsatellite markers, which were all that were available at the time. Although this strategy proved to be quite successful for the HLA region,\textsuperscript{50,51} the use of linkage analysis in families found no reproducible evidence of linkage outside the HLA region.\textsuperscript{52} The same problem came up in other multifactorial disorders.\textsuperscript{53} We now know that linkage is good at finding “Mendelian” genes that make large contributions to risk but is much less useful in settings such as psoriasis, where individual genes each make relative small contributions to disease susceptibility.\textsuperscript{54} While association studies are easier to conduct because there is no need to collect family members, they require far more markers to survey the genome in an unbiased fashion (approximately 500,000 markers for association, as compared with the approximately 300 to perform a linkage scan).

Fortunately, the Human Genome Project produced the necessary collection of markers as the new millennium arrived. Single nucleotide polymorphisms (SNPs) are subtle differences in the DNA code that normally exist between individuals. Shortly thereafter, the HapMap\textsuperscript{55} provided a dense map of millions of SNPs that could be phased (ie, sorted into maternal vs. paternal chromosomes). Concomitantly, microarray-based genotyping arrived on the scene, allowing up to a million SNPs to be tested at once. In 2006, we initiated the Collaborative Association Study of Psoriasis in order to perform a GWAS of psoriasis.\textsuperscript{56} Analyzing 438,670 SNPs on 1359 psoriasis cases and 1400 normal controls, we found significant associations at 3 genetic regions that had previously been associated with psoriasis (HLA-C, IL12B, and IL23R),\textsuperscript{48,57} with HLA-Cw6 producing by far the strongest genetic signal. Several lines of evidence suggest that HLA-Cw6 may be involved in antigen presentation to CD8+ T cells, whose migration into the epidermis appears to be required for the development of psoriatic lesions.\textsuperscript{58}

By studying 18 of the most highly associated regions from the discovery GWAS in an additional 5048 cases and 5051 controls, we also found 4 other genome-wide significant association signals that were novel: IL23A, TNFAIP3, TNIP1, and IL4/II13. IL23A encodes p19, a subunit that is specific to the cytokine IL-23 and that binds to 2 other proteins found in psoriasis-associated regions: IL-23R and IL-12B. IL23B encodes p40, a subunit of both IL-12 and IL-23. While IL-12 supports Th1 cells, IL-23 supports Th17 cells, which protect the skin and other epithelial organs like the gut.\textsuperscript{59} Notably, IL23R is also associated with Crohn’s disease,\textsuperscript{60} which is strongly clinically associated with psoriasis.\textsuperscript{61} IL-23 expres-
Psoriasis and the Genetics of CTCL

sion is increased in psoriatic lesions, but IL-12 expression is not, suggesting that IL-23 is the primary target of highly clinically effective antibodies that target p40 and are now US Food and Drug Administration approved to treat psoriasis.

Antibodies targeting TNF-α are also highly effective against psoriasis. Therefore, it is probably more than coincidental that 2 of the other genetic signals we found (TNFAIP3 and TNIP1) regulate TNF-α signaling through the nuclear factor (NF)-κB pathway by regulating assembly and degradation of various signaling components via ubiquitylation. The same pathway is used by Toll-like receptors, which recognize microbial agents through the innate immune system. Different genetic variants near TNFAIP3 are associated with rheumatoid arthritis, and both TNFAIP3 and TNIP1 are associated with lupus. Thus, these genes provide important new therapeutic targets for multiple autoimmune disorders.

IL4 and IL13 encode cytokines that support the development of Th2 cells. Psoriasis has traditionally been viewed as a "Th1 disease," and genetic defects in this region may help tip the normal Th1/Th2 balance toward Th1. We recently showed that interferon-γ produced by Th1 cells supports the production of IL-17 by antigen-presenting cells, helping to explain the co-occurrence of Th1 and Th17 cells in the inflammatory infiltrate of psoriasis and other autoimmune disorders. Thus, at least 4 of the variants uncovered by these studies (IL12B, IL23A, IL23R, and IL4/IL13) affect the cytokine milieu of psoriasis.

With the likely exception of HLA-Cw6, we have not yet found the causative genetic changes responsible for these association signals. Nevertheless, the genes contained within these regions fit very well with emerging concepts of psoriasis pathogenesis involving loss of immunologic tolerance (HLA-Cw6), IL-23–driven Th17 activation (IL12B, IL23A, and IL23R), dysregulated NF-κB signaling (TNFAIP3 and TNIP1), and Th1/Th2 imbalance (IL4/IL13). Current studies in our laboratories are focusing on identifying these variants and demonstrating their abnormal functions, and identifying additional susceptibility regions in larger samples. Interestingly, several of these new genes also appear to engage the NF-κB and IL-17 signaling pathways.

Cutaneous T-Cell Lymphoma and Psoriasis: Genetic Convergence?

With these observations in hand, let us now return to the specifics of known genetic abnormalities in CTCL, both germ-line and somatic. Notably, the HLA-DRB1*11 and HLA-DQB1*03 alleles form an MHC class II haplotype that has also been associated with another T-cell–mediated skin disease, alopecia areata. On the other hand, GWAS of follicular lymphoma and psoriasis both revealed significant associations with the MHC class I region, at or near HLA-C. It will be of interest to assess whether the disease-associated haplotype observed in follicular lymphoma extends to include HLA-Cw6. The HLA-DRB1*11-DQB1*03 haplotype is not in extended linkage disequilibrium (LD) with HLA-Cw6, so it is very unlikely that these 2 lymphoma-associated regions will prove to be on the same haplotype. Nevertheless, the HLA class II association observed for MF fits well with the fact that the malignant clone is CD4+ in almost all MF cases, whereas the MHC class I association of psoriasis is congruent with the reported requirement for CD8+ T-cell entry into the epidermal compartment in order to trigger the psoriatic epidermal response.

Beyond the MHC, it is worthy of note that some of the germ-line variations associated with psoriasis and many of somatic mutations found in CTCL are predicted to influence signaling through the NF-κB pathway, including TNFAIP3 and TNIP1 in psoriasis and Bag4, Btnc, Nkiras2, Fsmd3, and Traf2 in CTCL. Other points of divergence, such as IL4/IL13 and IL12B/IL23A/IL23R variation in psoriasis not yet reported for CTCL, may prove to relate to the aforementioned differences in cytokine milieu between the 2 disorders.

In addition to germ-line variation and somatic mutation, it is also important to consider epigenetic changes in both psoriasis and CTCL. Thus, in addition to frequent deletions within the long arm of chromosome 10 containing the CD95 gene, alterations in methylation have recently been shown to accompany the marked downregulation of CD95 (Fas) gene expression that is consistently observed in CTCL, resulting in resistance to FasL-mediated apoptosis.

Conclusion

Despite its unparalleled accessibility, human skin, and especially inflamed human skin, is a very complex multicellular tissue. Looking ahead, it is going to be increasingly important to be able to study defined cell populations taken directly from the milieu of diseased skin tissue if we are to be able to analyze either genetic or epigenetic changes that contribute to the cutaneous manifestations of both psoriasis and CTCL. Indeed, it is precisely this experimental hurdle that explains why most genomic studies of CTCL to date have involved SS rather than MF. Tools that are very useful for this purpose include laser capture microdissection, direct gentle enzymatic dissociation of cells followed by microscale immunopurifications and cell sorting, and the development of methods for physiologically neutral expansion of the living cells derived from fresh tissue. As these tools become more optimized and more widely available, we can expect to enjoy many new insights into the genetics and biology of both psoriasis and CTCL.

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Clinical Trials in Cutaneous Lymphoma

Lessons Learned From the Systematic Evaluation of Cutaneous T-Cell Lymphomas at the National Cancer Institute and the Roadmap for Future Studies

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Introduction

Mycosis fungoides (MF) and Sézary syndrome (SS) are the major types of T-cell lymphomas that arise in the skin. Mycosis fungoides was first described by Alibert in 1806,1 and the cutaneous manifestations of plaques, tumors, and generalized erythroderma were well described by early 1900s.2 Sézary syndrome, first described by Sézary in 1938, is characterized by generalized erythroderma and circulating atypical lymphocytes that have the same convoluted nuclei in the blood as in the skin.3,4 After Crossen et al demonstrated that Sézary cells and mycosis cells were lymphocytes,5 monoclonal antibodies (MoAbs) to lymphocyte antigens showed that they arise from the T helper subset of T lymphocytes.6,7

We and others subsequently showed that these Sézary/mycosis cells were monoclonal helper T cells with specific T-cell gene rearrangements.8-10 These findings were incorporated into the revised lymphoma staging classification. Systematic staging studies performed in the 1970s and 1980s gave rise to the current tumor-node-metastasis (TNM) staging classification. Many of the treatment approaches to other low-grade non-Hodgkin lymphomas (NHLs) have been tested in the cutaneous lymphomas, where they also have activity. A number of novel therapies have now been approved specifically in cutaneous T-cell lymphoma (CTCL). Multiagent chemotherapy does not cure CTCL and does not prolong survival compared with the sequential use of single agents. Combined-modality therapies with biologic agents and new agents are increasingly being used, but their effect on survival has not been demonstrated in prospective controlled trials. The underlying molecular abnormalities of CTCL are heterogeneous and remain to be defined, although there has been progress in the past 10 years. Systematic development of a large panel of cell lines and pure population of many cases Sézary cells is needed. Tissue microarrays could be established from skin and lymph node biopsies.

This article describes work originally conducted at the National Cancer Institute (NCI)-Veterans Affairs (VA) and NCI-Navy Medical Oncology branches and how future studies could take maximal advantage of the knowledge gained. This is not meant to be an exhaustive review, but rather a look back at the contributions of a single group and suggestions for future directions. We have not provided a complete list of contributions or references and apologize to the many great investigators who have contributed to the field.

The National Cancer Institute Veterans Affairs Medical Oncology Branch

Investigators in the Dermatology Branch of the NCI, including Marvin Lutzner and Richard Edelson, collected a series of cases with SS exploring the electron microscopic appearance of the cells and later exploring the immunologic properties of their cell surface antigens.7 At this time, in the early 1970s, the Medicine Branch of the NCI undertook serial staging studies and therapeutic studies of other predominantly B-cell NHLs. When Drs. John Minna, Adi Gazdar, Paul Bunn, and Dan Ihde were recruited by the NCI to establish a lung cancer research program at the VA Hospital in Washington, DC, it was elected to also undertake a systematic study of T-cell lymphomas. Joining these efforts were physicians already at the VA, including pathologists Mary Matthews and John Guccon, hematologist Geraldine Schechter, and dermatologist A. Betty Fischmann. Many of the fellows at the NCI participated in these studies, including Desmond Carney, Bernard Poiesz, Francine Foss, Steven Rosen, Charles Winkler, Frederick Kaye, Edward Sausville, Bruce Johnson, Larry Posner, Doug Blayney, Mark Huberman, Brian Brigham, and Ethan Dmitrovsky. Patients with CTCL were sought for clinical trials.

Systematic Attempts to Establish Human Tumor Cell Lines

A major translational research goal of the Branch was to establish human cell lines from patient biopsies. Sequential cell lines were initially labeled as human tumor (HUT)-1, HUT-2, and so on. Later these cell lines were relabeled as NCI-H1, NCI-H2, and so on. Tumor samples were collected primarily from patients with lung cancer and CTCL, the major tumor types under investigation.
Permanent cell lines were more difficult to establish from patients with CTCL compared with those with lung cancer. However, after several years, some permanent cell lines were established.\textsuperscript{11-13} About the same time, other investigators had described the antigens expressed by various subsets of lymphocytes and had established that T-cell growth factor (later termed interleukin [IL]-2) could potentiate the growth of T lymphocytes.\textsuperscript{14} Sézary cells and MF cells taken directly from patients and cultured cell lines such as HUT-78 and HUT-102 were shown to express T-helper antigens, to have T-cell receptor (TCR) gene rearrangements, and to proliferate in response to IL-2 confirming their T-cell origin.\textsuperscript{13-15}

These observations raised the question as to whether the established cell lines were secreting IL-2 in an autocrine manner. The laboratory of Robert Gallo, and Frank Ruscetti with NCI fellow Bernard Poiesz, collaborated in these investigations. For many years, Dr. Gallo’s laboratory had been searching for human retrovirus that might cause cancer. Dr. Poiesz used 1 of our cell lines (HUT-102, NCI-H102) as a control for 1 of his reverse transcriptase assays. Fortuitously, he found a high reverse transcriptase signal in HUT-102. Electron microscopic studies confirmed the presence of viral particles, and the human T-cell lymphoma virus (HTLV-1) was isolated from the cell line.\textsuperscript{16} The subject from which the virus was derived was a young black man from the Caribbean with a somewhat aggressive lymphoma.\textsuperscript{15}

**HTLV-Associated T-Cell Lymphomas and Adult T-Cell Lymphoma/Leukemia**

The discovery of HTLV-1 and the discovery of tests to detect HTLV in cells and anti-HTLV antibodies in serum\textsuperscript{17-22} led to clinical reports describing the major features of the disease.\textsuperscript{23-26} Generally, the clinical manifestations were considerably more acute and the progression of disease more rapid than with CTCL. Patients more often have visceral (stage IV) disease, and bone metastases with hypercalcemia are more frequent.\textsuperscript{15,24,25} The Japanese investigators who had described adult T-cell leukemia/lymphoma found evidence of HTLV-1 in most of these patients.\textsuperscript{26} Clusters of patients were also described in the southeastern United States and the Caribbean regions.\textsuperscript{25,27} Frequent involvement of skin, blood, bone, and nodes were common features.\textsuperscript{20-27} The frequent cytogenetic abnormalities seemed to be similar between US and Japanese cases, including aneuploidy and 14q11 changes.\textsuperscript{28,29}

**HUT-78 and HIV**

Dr. Gallo’s laboratory was also interested in determining whether HIV/AIDS was caused by HTLV-1 or a similar T-cell tropic retrovirus. Our cell line HUT-78 was shown to lack all evidence of human retrovirus. However, HUT-78 (labeled H-9 by Dr. Gallo’s laboratory) turned out to be an excellent cell line for propagation of the HIV viruses isolated from France and, later, the United States.\textsuperscript{30-34} This discovery allowed the development of assays to detect and propagate HIV.\textsuperscript{35-37} These T-cell lymphoma cell lines have formed the scientific basis for the analysis of many features of T-cell malignancies, including aneuploidy, cytogenetic abnormalities, and gene expression abnormalities. Subsequent studies confirmed that the CTCL cell lines produced and responded to the T-cell growth factor IL-2, the original hypothesis.\textsuperscript{14} T-cell lymphomas are a very heterogeneous set of lymphomas; therefore, systemic study would be aided by a larger panel of cell lines. Unfortunately, after the NCI-VA Branch stopped attempts to establish such cell lines, few new cell lines have been established. Such efforts should be re-established.

**Systematic Staging of Cutaneous T-Cell Lymphoma**

Systematic staging of Hodgkin disease and B-cell NHL was becoming common in the mid-1970s, with patients routinely undergoing lymphangiograms (later, computed tomography [CT] scans), lymph node biopsies, bone marrow biopsies, liver biopsies, and sometimes laparoscopy or laparotomy with multiple biopsies. Assessment of peripheral blood for malignant cells was also undertaken. Earlier studies had shown that mycosis cells could spread to lymph nodes, blood, liver, bone marrow, and other organs.\textsuperscript{2,4} Extracutaneous spread to these sites was generally associated with a worsened prognosis. However, the staging classifications at the time generally revolved around the type of skin lesions, with limited plaques having the best prognosis followed by generalized plaques, tumors, and generalized erythroderma. Visceral organ involvement was designated as stage IV with a poor prognosis. Investigators at the NCI undertook a systematic staging of consecutive patients with CTCL that included complete physical examination, microscopic evaluation of the peripheral blood, lymph node biopsy, lymphangiography, laparoscopy with liver biopsy, and bone marrow aspirate and biopsy.\textsuperscript{38-46} Peripheral blood was scored as positive or negative and by the absolute number of circulating Sézary/mycosis cells. Prognosis was shown to be related to the presence or absence of circulating cells and their absolute number.\textsuperscript{42-44} Lymph node biopsies were scored as normal (LN0), showing hyperplasia with architecture preserved and scant atypical cells (LN1), preserved architecture with more frequent atypical cells (LN2), somewhat distorted architecture with a predominance of atypical cells (LN3), or effacement of the architecture with a predominance of atypical cells (LN4).\textsuperscript{40} Prognosis correlated well with this classification.\textsuperscript{40,41}

These studies showed that involvement of peripheral blood and palpable lymph nodes almost always arose before involvement of internal nodes. This observation obviates the need for routine lymphangiography (and now CT scans) in patients with CTCL lacking palpable lymphadenopathy. Similarly, visceral organ involvement was extremely uncommon in the absence of lymph node or peripheral blood involvement. Visceral organ involvement was, of course, associated with a worsened prognosis.\textsuperscript{31,45,46} These findings led to the development of the TNM staging classification of CTCL, including MF and SS, with the T stage relating to the type of skin involvement; the lymph node staging system classifying LN0, 1, and 2 as not involved and LN3 and LN4 as lymph node involvement; and visceral involvement as M1. The T1-4, N0-3, and M0/M1 classifiers were then used to group patients into 4 stages as occurred with other cancers.\textsuperscript{11,47} This classification had undergone only minor modifications since it was proposed in 1979, with the exception of the definition of peripheral blood involvement. Initially, peripheral blood involvement was classified as B0 or B1 within each stage. More recently, the International Society for Cutaneous Lymphomas (ISCL)/
European Organization for Research and Treatment of Cancer group has revised these criteria. Sézary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sézary cells cannot be used to determine tumor burden, then 1 of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: expanded CD4+ or CD3+ cells with CD4/CD8 ratio 10:2 or expanded CD4+ cells with abnormal immunophenotype including loss of CD7 or CD26. A T-cell clone is defined by polymerase chain reaction or Southern blot analysis of the T-cell receptor gene. 

**Histologic Conversion**

Histologic conversion from a low-grade lymphoma/leukemia to a more aggressive form with an increase in cell size and proliferative rate was well described in low-grade B-cell leukemias and lymphomas, including chronic lymphocytic leukemia (where it was labeled “Richter’s syndrome”) and in follicular lymphomas. The NCI-VA Branch and other groups described histologic/cytologic transformation in patients with CTCL. Like the B-cell counterparts, this conversion was associated with an increase in size of the lymphocytes and their nuclei and an increased proliferative rate. Response to standard agents was low, and prognosis was poor. Bone marrow transplantation was attempted, but the results were poor. Multiagent chemotherapy produced some responses, but these were short lived. Optimal therapy for these patients remains to be defined. Recently, a high response rate has been reported with the use of pralatrexate. It will be important to understand the molecular/genetic changes that accompany this transformation so that more specific therapeutic approaches can be designed. 

**Therapy for Mycosis Fungoides and Sézary Syndrome**

**Topical Therapy**

By the mid-1970s, several types of therapy directed at the skin were in widespread use. These included local radiation, total-skin electron beam radiation (TSEBR), topical nitrogen mustard (and other cytotoxic chemotherapies), topical steroids, and ultraviolet (UV) light irradiation. The routine use of each of these therapies had major limitations. Local radiation therapy almost always improved target lesions, but other lesions invariably developed. Total skin radiation was not possible until the advent of electron beam therapy from linear accelerators and techniques to block sensitive areas from irradiation. Late skin toxicities, including telangiectasias, ulcers, and second skin cancers, were recognized.

Therapy with the whole-body application of nitrogen mustard (HN-2) was hampered by the frequent development of allergic reactions, the carcinogenic nature of HN-2 that required special handling, and the difficulties associated with whole-body application for uniform distribution and avoidance of sensitive areas such as the eyes and mucous membranes. A commercial product with HN-2 in Aquaphor has recently been developed.

Ultraviolet light irradiation required special instruments for whole-skin irradiation of UVA and UVB light. Subsequently, it was recognized that psoralens could potentiate the effects of UVA light, but oral psoralens have many toxicities and potentiate the cutaneous toxicities of phototherapy. UVB therapy does work in some patients with early patches and plaques. Combinations with biologic agents are routinely used. 

**Combined Total-Skin Electron Beam Irradiation and Chemotherapy**

Systemic chemotherapies such as antimetabolites like methotrexate and alkylating agents such as HN-2, cyclophosphamide, and chlorambucil were known to produce short-lived partial responses in a minority of patients. Combination chemotherapy was in its infancy. With this backdrop, investigators at the NCI undertook a series of clinical trials designed to determine if combined-modality treatment could produce sustained complete remission (CR) and ultimately improved survival in patients with CTCL. A Stanford group had developed techniques for TSEBR and had shown that it could induce CRs in a majority of patients. Unfortunately, these CRs were usually short lived, and relapse was inevitable. Combination chemotherapy had been shown to improve CR rates in patients with Hodgkin disease and diffuse large-cell NHL. The role of combined irradiation and chemotherapy in follicular lymphomas and CTCLs was less certain. The NCI-VA group treated a series of patients with CTCL with TSEBR combined with multiagent chemotherapy. The CR rate was high and related to disease stage, with higher CR rates in early stages. There were considerable toxicities with this combined approach, including skin desquamation, telangiectasias, neutropenia, total alopecia, nausea, vomiting, fatigue, and others. These promising results lead to a randomized trial comparing the combined-modality therapy to a simple strategy of single-agent topical therapy. Not surprisingly, the combined therapy was associated with a higher complete response rate and considerably more toxicity. Surprisingly, the progression-free and overall survival did not differ by the therapeutic arm. This was largely because patients on the combined arm were not cured and continued to experience relapse over time. Patients on the topical therapy arm had their disease controlled for many years by a series of single therapies. Similar results were observed in other low-grade B-cell NHLs where multiagent chemotherapy with or without radiation therapy failed to produce long-lasting CRs and cures.

**Biologic Agents and Combinations: Interferons**

The first biologic agents to show activity in NHL, including CTCL, were the recombinant interferons. These recombinant proteins required subcutaneous daily administration and were given in escalating doses that were associated with considerable toxicity. The most severe acute toxicities included a constitutional flu-like syndrome with fever, chills, malaise, and fatigue. These symptoms were most severe in the first few weeks of therapy, but gradually, some tolerance developed. Recombinant interferons α-2a and α-2b were shown to produce objective responses in a large fraction of patients. At the NCI, objective responses were reported in 29% of the patients, but these were rarely CRs, and all patients relapsed. Other interferons such as recombinant interferon-γ were also active in CTCL but had little advantage over other available IFNs. Pegylated interferons were later introduced so that the frequency of subcutaneous administration could be reduced. These interferons were approved for use in other indications. Although not approved...
for CTCL, this form of off-label therapy can be considered standard of care in CTCL, in our opinion.

The understanding that all lymphomas are systemic in nature and that topical therapies only attack the bulk of disease led to trials combining topical therapies such as psoralen and UVA (PUVA) with systemic therapies such as interferons and, later, retinoids. The combination of recombinant interferon plus PUVA produced high CR rates, especially in early stages, and the responses could be maintained even after the PUVA frequency was reduced and discontinued.60 The toxicity of this combination was considerably less than was reported with the combination of TSEBR and chemotherapy. Unfortunately, no randomized trial comparing the PUVA/interferon combination to either therapy alone was ever conducted. Several such randomized trials adding interferon to chemotherapy were conducted in other NHLs predominantly of B-cell origin. A meta-analysis of these trials demonstrated that recombinant interferons were associated with a significantly improved survival.61 Interferons were also combined with extracorporeal photopheresis, where the combination appeared to produce higher response rates compared with photopheresis alone.62 The combination of interferon with etretinate also seemed superior to etretinate alone, with responses reported in 28 of 45 patients (62%).63 No randomized trials comparing either alone with the combination were reported. There is also no clear evidence that the addition of interferon to chemotherapy is beneficial.59 Interferon-α mediates its biologic effects through activation of the JAK/STAT pathway. Sun et al developed an interferon-resistant clone of HUT-78R, that lacked STAT1 protein and mRNA, suggesting that resistance could be related to lack of STAT1 expression.64 In 2001, Rook et al reported that nearly 50% of 32 patients treated with recombinant IL-12 had an objective response.65

Recombinant Interleukin-2 Fusion Toxin: Denileukin Diftitox

Another class of biologic agents that received widespread study in CTCL was the recombinant IL-2 fusion toxin denileukin diftitox.66-69 This novel agent took advantage of the fact that CTCL cells express the IL-2 receptor (CD25) and therefore could deliver the toxin directly to the CTCL cells. Denileukin diftitox was studied in patients with biopsy-proven CTCL who were randomized to 9 mcg/kg/day or 18 mcg/kg/day for 5 consecutive days every 3 weeks for up to 8 cycles.66 Overall, 30% of the 71 patients had an objective response, and the response rate and duration were not different by dose. Toxicities included flu-like syndromes; acute infusion related events; a vascular leak syndrome with hypotension, hypoalbuminemia, and edema; and transient elevations of hepatic transaminase levels. Subsequent studies showed that acute toxicities could be decreased in frequency and severity by steroid premedication.67 Based on these results, denileukin diftitox was approved for use in this indication. Denileukin diftitox was subsequently shown to have higher objective response rates in patients whose tumors expressed a high level of CD25 (objective response, 79%) versus those whose tumors expressed low levels of CD25 (objective response, 20%).68 Denileukin diftitox was also combined with other therapies, including hexametene, but there were no randomized trials to indicate that the combination approach is superior to a sequential approach.69

Monoclonal Antibody Therapy

Many antibodies that react with T-cell and B-cell antigens were tested in patients with T-cell and B-cell NHL. Rituximab is a mainstay of therapy for patients with CD19+ B-cell NHLs, and several radiolabeled anti-B cell MoAbs have also been approved. The MoAbs that have received the most study in CTCL have been the anti-CD5 antibody T101,70-78 the anti-CD25 antibody anti-Tac,79-81 and the anti-CD4 antibody zanolimumab.82 Anti-Tac immunocugnates were also studied but have not been further developed.80,81

A report from Stanford described the results of treating 9 patients with CTCL with a murine anti-CD5 MoAb, among whom 4 had an objective response.70 In another report, there were no objective responses among 11 treated patients.71 Among all other studies that were not limited to CTCL, there were 5 responses among 46 patients.72,73 These studies were limited by the fact that the antibodies were murine and the fact that CD5 is rapidly internalized after binding. These facts led to the development of radiolabeled antibodies such as T101. Boven et al showed that iodine 125(125I)-T101 was selectively cytotoxic for human malignant T-cell lines.74 The radiolabeled T101 MoAb was first given to patients with CTCL in imaging studies after radiolabeling with iodine 131 (131I). These studies demonstrated that the radiolabeled antibodies localized in lymph nodes and other areas of disease.75-78 These observations led to a trial of intravenous 131I-T101, where objective responses were reported in 3 of 6 patients.89 Unfortunately, industry stopped further development. The anti-Tac antibody was studied primarily in HTLV-1–associated T-cell lymphomas, where there was 10-times higher CD25 expression.79 Some short-lived responses were noted, but like T101, a humanized form was not studied, and there has been no US Food and Drug Administration approval. The HuMax-CD4 MoAb (zanolimumab) was studied in 2 phase II studies in 47 patients with refractory CTCL given weekly infusions. Objective responses were reported in 15 of 47 patients (32%).82 In the high-dose group, the response rate was 56%, with a median response duration of 81 weeks. Toxicities included low-grade infections and rash. This agent is undergoing further development after having been dropped by its manufacturer.

Adenosine Analogues

It has been appreciated that adenosine deaminase deficiency leads to immunodeficiency. We and others reported that malignant T cells have aberrant adenosine metabolism, making them sensitive to purine analogs.83,84 These observations led to studies of several adenosine analogues, including deoxycoformycin,85-88 fludarabine,89 and chlorodeoxyadenosine.90,91 For deoxycoformycin, responses were reported in 26 of 63 patients (41%). Deoxycoformycin was also combined with interferon, where Foss et al reported responses, but there seemed to be little advantage over each agent given individually.92

Fas/Fas Ligand

Fas (CD95) is a cell-surface receptor that, when activated by Fas ligand, induces apoptosis. There is evidence that CTCL cells are resistant to apoptosis. Wu et al showed that Fas expression is generally low in CTCL.93 They showed a direct correlation between Fas expression and Fas-mediated apoptotic sensitivity in CTCL. Uregulation of Fas restored sensitivity to apoptosis. Similar data
Systemic Evaluation of CTCLs at the NCI

were published by Meche et al, who showed that there was a relationship between low Fas and resistance to apoptosis in SS. The development of Fas and Fas ligand therapy has been hampered by the high level of expression in the liver, leading to fatal hepatic necrosis. However, adenoviral delivery of Fas is still being evaluated in preclinical models.

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The authors have no relevant disclosures to disclose.

References
Introduction

In a perfect world almost all medical treatment decisions would be based on statistically significant data collected in randomized clinical trials. Well-defined assessment methods and endpoints are needed in order to compare new drugs with data and endpoints that are collected in a uniform manner. Sharing of data across international boundaries would also help to ensure that new drugs would become more freely available without local restrictions. In addition, with the sequencing of the human genome completed, it should be possible to determine in advance whether a patient will respond to an agent before its administration. In the absence of clinical trials, the use of a drug for an off-label orphan indication should be encouraged and reimbursed, regardless of whether there is a labeled indication. This article will review steps for new drug approval in the United States at this time, and discuss a rational approach and future directions to the conduct of clinical trials for cutaneous T-cell lymphoma (CTCL).

Drug Development

In the United States there is a required pathway for developing a drug for use in humans. Before entering a clinic, evidence of the effect of this drug is collected in preclinical experiments in cell lines, ex vivo tumors, and xenograft models where feasible. High-output screening of drugs can incorporate biologic activity in the selection process. If a drug is of interest, toxicity studies must first be performed in animals and bacteria before minimal dose toxicity in humans can be estimated. Normal human volunteer studies are then performed to study drug pharmacokinetics and clearance before clinical efficacy studies. A new drug application (investigational new drug [IND]) is then filed by the investigator to the US Food and Drug Administration (FDA), and a series of clinical studies and discussions precedes drug approval before its administration. In the absence of clinical trials, the use of a drug for an off-label orphan indication should be encouraged and reimbursed, regardless of whether there is a labeled indication. This article will review steps for new drug approval in the United States at this time, and discuss a rational approach and future directions to the conduct of clinical trials for cutaneous T-cell lymphoma (CTCL).

Types of Clinical Trials

Pilot Studies. Pilot studies are helpful when there is no information about the response rate of a drug in a disease where there could be a biologic effect. Pilot studies enroll only a small number of patients, usually 10-20, who are not randomized, and are descriptive in nature. They are often investigator initiated. Their small size precludes randomization or use of a placebo arm, though it may be possible to use a vehicle control in topical half-body design. Pilot studies are also used to assess the preliminary efficacy of an approved drug, when used for another indication. Pilot studies can also be used as the front end of a stage I/II trial in a 2-tier Simon design.1

Phase I and III Clinical Trials. The primary goal of all phase I trials is to determine drug toxicity and safety, and to identify the maximum tolerated dose (MTD) of a new drug. The most common design is a dose escalation with cohorts of 3 patients sequentially enrolled at increasing doses. Generally, the first dose selected is well below the toxicity seen in preclinical animal studies. If an adverse event occurs that is thought to be related to the drug, the cohort of 3 is usually expanded to 6 patients to see if the event reoccurs. Examples of CTCL phase I and II clinical trials are shown in Table 1.2-5

When a dose-limiting toxicity (DLT) appears, the MTD is the dose level below it and is used to study a larger final cohort, for example a phase II Simon design.1 Phase II trials are used to determine an optimal dose that is safe and identify a preliminary response rate. The Simon design has an interim analysis built into it after a predetermined number of patients have been treated. If there is insufficient evidence of efficacy, the trial is terminated for reasons of futility. This approach prevents patients from being exposed to ineffective agents and saving time and expense. The time for the interim analysis (generally after 12-15 patients have enrolled and reached a certain time point) will depend upon the estimated response rate that also determines the final numbers of patients to be enrolled. Phase II trials require much smaller numbers of patients than phase III trials.

Two phase II 1-arm clinical trials conducted with similar findings were accepted by the FDA for both registration of bexarotene...
(early- and late-stage patients)6,7 and vorinostat for CTCL2,8 Phase II randomized trials are built on the assumption that there exist 2 equal populations of patients, 1 of whom with received treatment, and the other who will receive either no treatment (placebo) or standard of care. They assume that treatment will affect either survival, response rate, or be safer or less expensive. The future randomized trial for FDA approval will compare the old drug versus the new drug head-to-head, or a combination of old drug plus new drug versus the old drug as monotherapy. This has been called the beat them or join them approach to drug development (Owen O’Connor, personal communication). If a new active drug is to be compared with a placebo, the trial may contain a crossover design whereby patients who are randomized to placebo receive active drugs if they progress or have stable disease (SD) after a defined treatment period.

**Phase III Trials.** Phase III clinical trials represent the gold standard for drug development, and their size is based on appropriate statistically powered primary endpoints with additional secondary endpoints. These trials are required to be randomized with at least 2 arms, of which 1 can be a placebo or standard of care and the other can be the new drug or procedure. In order to find a statistical difference between arms, high numbers of patients (hundreds) are required, and must vary depending on the response rate. Because of the rare incidence of CTCL, only 2 randomized phase III clinical trials have been completed with systemic therapies, as shown in Table 2.9,10 Both took over 10 years to accrue.9 A third double-blind placebo-controlled phase III trial was conducted and randomized patients to topical vehicle versus topical peldesine cream.11 No difference was found between the 2 arms, suggesting the beneficial effects of topical glycerin vehicle for early mycosis fungoides lesions.

**Phase IV Trials.** Phase IV trials are conducted after a drug is approved by the FDA. Some are mandated by the agency when preliminary approval of a drug is granted, in order to provide additional safety or efficacy information, and must be completed to gain full approval. The majority of phase IV studies are investigator-initiated trials in new indications or in novel combination with other agents. Phase IV studies can be driven by marketing and the need for other investigators to gain experience with a new drug. They are also conducted in order to better manage drug side effects, and often lack statistical significance in their design.

### Practical Issues in Cutaneous T-Cell Lymphoma Clinical Trials

**Design of Primary and Secondary Clinical Endpoints**

Zacheim et al brought attention to adherence to defined endpoints for the conduct of CTCL trials back in 1996.12 Bexarotene6,7 and vorinostat2,8 were approved on the basis of skin improvement by > 50% as the primary clinical endpoint but used different measurement tools. Progress is being made through the International Society of Cutaneous Lymphomas (ISCL) in developing well-defined consensus clinical response and endpoint criteria to allow standardized comparisons between different agents (Olsen, personal communication). These incorporate skin score into a composite score such as the one used in the approval of romidepsin. The modified skin-weighted assessment tool (mSWAT) is a primary clinical endpoint first used to measure skin involvement in denileukin diftitox trials.10 It should be combined with clinical measurements of nodes, blood, visceral disease to assess systemic effect, ie, a global assessment of complete response (CR), partial response (PR), SD, and progressive disease (PD). In a global assessment, if there is disease progression in any of the compartments, then the effect is PD. Alternatively, all sites must have a complete remission for a CR designation. A skin biopsy should also be performed to confirm CR in skin. An index lesion evaluation, utilizing specifically designated skin lesions such as the composite index lesion assessment,6 should only be used to assess effects of topical agents applied to specific skin lesions because the patient might progress outside of the graded areas index lesions.

Secondary endpoints may include time to response, duration of response, time to progression, symptoms, and assessments of quality of life. Erythema is sometimes given its own score and remains a key variable for assessing skin response. However, erythema can be ephemeral, and better ways of measuring erythroderma can be developed using technology. Finally, standards for assessing evaluable subjects or intent to treat analysis should be determined because responses will be lower in the latter group.

Another issue that should be addressed in clinical trials are the definitions of relapse (new lesions after a CR), loss of response (mSWAT score above the initial PR value), and PD. Progressive disease may be defined differently depending on whether the patient has achieved a response or not. If a patient has not responded, then PD is defined as a > 25%-50% improvement in the baseline mSWAT score and SD as < 25% worse from baseline. If the patient has responded, then a PD is best defined relative to the nadir rather than the beat them or join them approach.
### Rational Clinical Trial Design in Cutaneous Lymphoma

**Selection of Ideal Patients for Clinical Trials**

In order for clinical trials to be conducted, enough of the right patients must agree to participate and give written consent. It is much more likely that a patient will participate if they have failed multiple other therapies, have limited treatment options, or lack the health care insurance needed to afford new expensive drugs. This is more common for patients with advanced stages of CTCL. Furthermore, patients must be able and agree to make specified visits, sometimes at great inconvenience and cost. Conversely, drug developers want their therapeutic agents to have a low rate of complications and adverse events to show the safety of their agent. The patients they wish to include in clinical trials may be difficult to identify, or for some studies, simply do not exist because of the strict eligibility criteria.

The perfect patient to enroll in a clinical trial is a relatively young and healthy individual who lacks all comorbidities, has normal laboratory tests, and has not been heavily treated. The median age of a patient with CTCL is 65 years, which is both good (it helps to be unemployed or retired to have the time to participate), and bad (increased comorbidities and drugs are common). To be a research subject, it helps to have financial stability, live close to a medical center, and be able to travel conveniently to frequent study visits.

Some of the difficulties particular to patients with CTCL are also noteworthy. The patients must have just the right type and number of previous therapies, and must be able to be off all therapy for up to 4 weeks before initiation of most studies. This washout may be required even if their disease is progressing or will progress without therapy for a month and be thrown out of the trial quickly for PD or symptoms. In some trials, patients also have to be taken off of palliative topical steroids that they cannot tolerate. If a composite index lesion score is to be used, the patients must have very well-circumscribed lesions that are not allowed to run into others and are photogenic. It is important that patients with different stages and variants of CTCL be equally distributed between 2 arms in a trial. For trials randomized to standard of care, it should be noted that no standard of care exists for CTCL, and any study population will have heterogeneous treatments or a sequence of treatments in the past. Eligibility criteria are often too strict to enroll the majority of CTCL patients, especially patients who cannot tolerate washout or stay off of topical therapy. Many patients have received multimodality therapies. In summary, ideal CTCL clinical trial patients are relatively rare because of stringent eligibility criteria. The ones who are eligible to participate in the studies will not necessarily be the same as those taking a new drug. More rational guidelines could be incorporated into CTCL clinical trial design to make eligibility and accrual more realistic.

### Future Directions in Cutaneous T-Cell Lymphoma Clinical Trials

#### Post-Trial Surveillance

The most common chemotherapy used for patients with advanced CTCL is probably cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP), but it has never been tested in a randomized trial for CTCL. Other combination chemotherapies are also used and may give results that are short-lived or perhaps lead to disease progression. Long-term follow-up data after the end of treatment would be helpful in determining the consequence of single and also of sequential therapies on the patient’s immune system and survival. We need to know whether the overall survival in patients is caused by or influenced by our treatment selection.

#### Wish List for Trials

We need to start with comparisons of commonly used agents that lack FDA approval but that are important for our patients. For example, one of the most active agents for CTCL, interferon-α, has not been studied in a comparison trial, and is not FDA approved, making it difficult to get reimbursed. Secondly, preclinical studies have identified synergist combinations that also deserve to be studied in trials. I have outlined some ideas in Table 3. As new agents are introduced, it will be important to incorporate them appropriately into clinical use and to test combinations with other agents in whole trials rather than in single patients. Many of the CTCL specialists use

---

**Table 3 Wish List for Basic Clinical Trials**

<table>
<thead>
<tr>
<th>Treatment 1</th>
<th>Treatment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorinostat plus lower doses of PUVA or radiation</td>
<td>Vorinostat plus bexarotene</td>
</tr>
<tr>
<td>Pegylated interferon-α once per week versus interferon-α 2b daily</td>
<td>Pegylated interferon-α daily versus ECP plus interferon-α 2b once per week</td>
</tr>
<tr>
<td>Vorinostat plus interferon-α</td>
<td>ECP versus ECP plus interferon-α</td>
</tr>
<tr>
<td>Bortezomib plus vorinostat</td>
<td>Interferon-α alone versus ECP plus interferon-α 2b once per week</td>
</tr>
</tbody>
</table>

**Wish List for Trials**

- Vorinostat plus lower doses of PUVA or radiation
- Vorinostat plus bexarotene
- Pegylated interferon-α daily versus ECP plus interferon-α 2b once per week
- ECP versus ECP plus interferon-α 2b daily
- Interferon-α alone versus ECP plus interferon-α 2b once per week
- Pegylated interferon-α 2b daily versus interferon-α 2b once per week
- Vorinostat plus interferon-α
- First line: acitretin (or isotretinoin) versus bexarotene
- Bortezomib plus vorinostat
- Vorinostat plus lower doses of PUVA or radiation

Abbreviations: ECP = extracorporeal photopheresis; PUVA = psoralen and ultraviolet A therapy
both skin-directed and systemic therapies to optimize the response of their patients, as we have reported.13-15 Examples include phototherapy or photopheresis plus interferon or retinoids.16

Miscellaneous Comments

Every patient with CTCL has a different T-cell clone (or clones), and progression probably involves an accumulation of many individual genetic mutations that are now possible to define using comparative genomic hybridization or future deep sequencing. Thus, to make progress in selecting the most effective therapy for each patient, it is crucial to collect tumor specimens at baseline and during the course of disease, especially with progression. These specimens should be used for translational studies such as immunohistochemistry, in situ hybridization, mRNA expression, and comparative genome hybridization arrays to develop biomarkers for response or progression. Key genetic pathways represent ways to target the malignant cells specifically without toxicity or immunosuppression. Because line sepsis is so common and deadly in patients with advanced CTCL, oral therapies are safer than infusions. However, insurance may be more willing to reimburse infusions over pills, and the latter reimbursements are subject to the Medicare donut hole after only days to weeks. When CTCL is treated by oncologists, the norm is to give a course of therapy and then stop and wait. Unfortunately, CTCL almost always comes back, so therapy is best tapered slowly when a maintained CR is reached. In general, CTCL is a chronic disease that requires constant treatment and maintenance after any definitive therapy.

Conclusion

We must all collaborate if we are to conduct high-quality and rational clinical trials to make progress. The same well-defined endpoints for comparing efficacy between agents should be required. Phase II trials that are randomized with statistical power and futility analysis are the gold standard for the development of new drugs. Rational inclusion/exclusions should be realistic for the patients who will ultimately use the drugs so that they can participate in clinical studies.

Disclosures


References

New Strategies to Optimize Outcomes in Patients With T-Cell Lymphoma

Jasmine Zain, Owen A. O’Connor

Clinical Lymphoma, Myeloma & Leukemia, Vol. 10, Suppl. 2, S84-S87, 2010; DOI: 10.3816/CLML.2010.s.014

Keywords: Aggressive B-cell lymphoma, CHOP therapy, CTCL, Pralatrexate, Methotrexate

Background

Mature T-cell and natural killer (NK) cell non-Hodgkin lymphoma (NHL), also called peripheral T-cell lymphomas (PTCLs), comprise about 12% of all NHLs showing great morphologic diversity and histologic variation.1 The current 2008 World Health Organization classification2 recognizes over 20 types of mature T-cell and NK T-cell lymphomas, as listed in Table 1. Cutaneous T-cell lymphomas (CTCLs) are T-cell lymphomas that arise in the skin and are classified as a separate entity based on their distinct clinical behavior and prognosis.3 For aggressive lymphomas, a T-cell phenotype confers a worse clinical outcome compared with B-cell lymphomas, with the exception of ALK-positive anaplastic large-cell lymphoma. Long-term survival at 5 years remains at 10%-30% for most histologies with current treatment strategies, as compared with 55% for diffuse large B-cell lymphoma.4 Advanced disease stage, high International Prognostic Index at presentation, and inherent chemoresistance contribute to this dismal outcome.5,6 Most patients are treated with CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone)/CHOP-like regimens as the first line of therapy adopted from the management of aggressive B-cell lymphomas, but the outcome remains poor.7 Relapsed and chemoresistant disease remains a significant clinical dilemma in the care of these patients. The rarity and heterogeneity of these diseases makes it difficult to do well-conducted clinical trials; hence, there are no well-defined standards for the treatment of these diseases either in the first-line setting or for relapsed disease. There is a need to develop new targeted treatment options for these patients based on an understanding of the pathogenesis of these lymphomas. Emerging new therapeutic agents for the treatment of relapsed/refractory PTCL are described herein.

Pralatrexate

Pralatrexate (PDX, 10-propargyl-10-deazaaminopterin), is an exciting new antifolate that has recently been granted approval by the Food and Drug Administration (FDA) for use in the treatment of relapsed and refractory peripheral T-cell lymphomas.8 Pralatrexate has been rationally designed to have a 10-fold higher affinity for the 1 carbon-reduced folate carrier (RFC-1) as compared with methotrexate (MTX).9 The structural differences between PDX and MTX are highlighted in Figure 1. In initial cytotoxicity assays, PDX was found to be 5 times more potent as an inhibitor of growth of cells in comparison with MTX across a variety of cell lines including human breast cancer, non–small-cell lung cancer, mesothelioma, and several human lymphoma cell lines.10 Preclinical animal data using xenograft models of lymphoma have confirmed the superior efficacy of PDX as compared with MTX in inducing tumor responses.11 Early clinical data established the activity of PDX in T-cell lymphomas as compared with B-cell lymphomas.12 It is also established that an elevation in the pretreatment level of homocysteine and methylenalonic acid is associated with a higher incidence of stomatitis. Hence, normalization of homocysteine and methylenalonic levels with folic acid and vitamin B12 supplementation is recommended to reduce the severity of mucositis in patients receiving PDX. The activity of PDX in T-cell lymphomas has now been confirmed by a phase II trial, as described below, that has led to the FDA approval of this agent.

The PROPEL (Pralatrexate in Relapsed or Refractory Peripheral T-Cell Lymphoma) trial is the largest prospective single-arm multicenter study of the use of PDX in patients with relapsed or refractory aggressive PTCL.8 All histologies of T-cell NHL were eligible for the study, including transformed mycosis fungoides, and the rare forms of NK T-cell lymphomas. Out of the 115 patients who were enrolled between August 2006 and April 2008, 109 were evaluable. This was a heavily pretreated population with a median of 3 previous treatment regimens (range, 1-12) including 18 patients with a previous autologous transplantation (ASCT). A total of 53% of patients were refractory to the last regimen. In addition, 25% of the patients never had a response to any therapy, indicating a refractory state. Treatment schedules consisted of PDX given at 30 mg/m² weekly for 6 weeks followed by 1 week of rest in a 7-week cycle. Based on an independent central review, the overall response rate (ORR) for all patients by International Workshop Criteria (IWC; complete response [CR] plus unconfirmed complete response [CRu] plus...
Histone Deacetylase Inhibitors

Histone deacetylase inhibitors are epigenetic agents found to be active in the treatment of T-cell lymphomas. Two agents of this class, vorinostat and romidepsin, are approved for the treatment of CTCL in the United States. The various classes of HDACIs are listed in Table 2.

Histone deacetylase inhibitors work by a myriad of different mechanisms including the following: (1) alteration in the expression of genes that regulate cell cycle–like upregulation of p21/p27, and downregulation of cyclin D; (2) acetylation of nonhistone proteins including signal transducer and activator of transcription (STAT3), RelA p65 and p53, HIF-1α, and immune modulation (LAIR1, GUCY1A1, ANGPT1). A brief description of the various HDACI currently in clinical use or trials for T-cell malignancies is listed below.

Romidepsin (depsipeptide, FK228) is cyclic peptide originally isolated from the broth culture of Chromobacterium violaceum that is currently approved for the treatment of patients with CTCL who have failed at least 1 previous systemic therapy. Two phase II trials of intravenous romidepsin in patients with relapsed PTCL have shown impressive activity. The National Cancer Institute sponsored trials for T-cell malignancies is listed below.

Table 1  Classification of Mature T-Cell Lymphomas: World Health Organization 2008

<table>
<thead>
<tr>
<th>Classification</th>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell prolymphocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>T-cell large granular lymphocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>Indolent large granular NK-cell lymphoproliferative disorder (provisional)</td>
<td></td>
</tr>
<tr>
<td>Aggressive NK-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Systemic EBV + LPD of childhood</td>
<td></td>
</tr>
<tr>
<td>Hydroa vacciniforme-like lymphoma</td>
<td></td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, unspecified</td>
<td></td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td></td>
</tr>
<tr>
<td>Anaplastic large-cell lymphoma, ALK positive</td>
<td></td>
</tr>
<tr>
<td>Anaplastic large-cell lymphoma, ALK negative</td>
<td></td>
</tr>
<tr>
<td>Extramedullary NK/T-cell lymphoma, nasal type</td>
<td></td>
</tr>
<tr>
<td>Enteropathy-associated T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma (α/β only)</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous λ/δ T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Mycosis fungoides and Sézary syndrome</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous CD30+ T-cell LPD</td>
<td></td>
</tr>
<tr>
<td>LyP and primary cutaneous ALCL</td>
<td></td>
</tr>
<tr>
<td>Small/medium CD4+ cutaneous lymphomas (provisional)</td>
<td></td>
</tr>
<tr>
<td>Aggressive CD8+ epidermotropic cutaneous T-cell lymphoma (provisional)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALCL = anaplastic large-cell lymphoma; EBV = Epstein-Barr virus; LPD = lymphoproliferative disease; LyP = lymphomatoid papulosis; NK = natural killer
Median duration of response was 9 months with a time to progression of 12 months. Responses were seen across all histologic subtypes of PTCL. The dose was 14 mg/m² given on days 1, 8, and 15 of a 28-day cycle. We are currently awaiting the results of another trial of romidepsin in PTCL, sponsored by Gloucester Pharmaceuticals. The most common side effects were nausea, fatigue, anorexia, and leukopenia. The serious drug-related adverse effects seen in 2% of the patients were supraventricular tachycardia, infection, and neutropenia. In CTCL, pooled analyses from 2 phase II trials established an ORR of 41%, a CR rate of 7%, and a duration of response of 14.9 months. The ORR was 58% in patients with Sézary syndrome. Relief of pruritus was seen in > 60% of the patients.

In the United States, oral suberoylanilide hydroxamic acid (Zolinza®; vorinostat) 21 is approved for the treatment of CTCL in patients who have failed at least 2 previous systemic therapies at a dose of 400 mg/day. Panobinostat and belinostat are other HDACIs that are currently being investigated in the treatment of T-cell malignancies.

**Forodesine**

Forodesine is a transition state purine nucleoside phosphorylase inhibitor (PNP) that leads to apoptosis and proliferation blockage of lymphocytes. Forodesine has shown in vitro activity against chronic lymphocytic leukemia (CLL), NHL, T-lineage acute lymphoblastic leukemia (T-ALL), B-lineage acute lymphoblastic leukemia (B-ALL), and synergy with other anti-lymphoma therapeutic agents. Furman et al treated 34 patients with T-ALL using oral Forodesine and demonstrated a 32.4% RR including a 20% CR rate. 22 In CTCL, Duvic et al have reported an ORR of 39% in heavily pretreated patients in a small 36-patient study. 23

**Lenalidomide**

Lenalidomide (CC-5013), a second-generation analogue of thalidomide, is an immunomodulatory agent with biologic effects that include activation of NK cells and T cells, modulation of various cytokines such as tumor necrosis factor (TNF-α), interleukin-12, and interferon-γ in the tumor microenvironment and inhibition of angiogenesis. It has also been shown to have direct antitumor activity. A phase II trial of lenalidomide in PTCL was reported by Dueck et al (in abstract form) that enrolled 24 patients with mature T-cell lymphomas. 24 The ORR was 34% with no CRs. Major side effects included dose-related myelosuppression, fatigue, pruritus, and rash. Deep vein thrombosis is rarely reported in trials in which lenalidomide is used as a monotherapy, but the incidence is much higher when combined with dexamethasone.

**Agents Targeting Apoptotic Pathways**

Apoptotic pathways are intricately controlled by a balance between proapoptotic (Bax, Bak, Mtd/Bok) and antiapoptotic proteins (BCL-2, BCL-XL, MCL-1, BCL-w). Small molecules such as gossypol analogues including AT-101, ABT-737, and the oral agent ABT-263, represent agents that can target antiapoptotic BCL-2 family members. In human tumor cells, ABT-263 induces Bax translocation, cytochrome c release, and subsequent apoptosis. This agent is now in clinical trials in CLL and in lymphoid malignancies. Patients are dosed on days 1-14 of a 21-day cycle with ABT-263 (dose range, 10-440 mg). One patient with NK T-cell lymphoma showed a 75% reduction of his skin lesions after cycle 2. The main toxicities so far include thrombocytopenia and elevation of LFTs.

**Proteasome Inhibitors**

Proteasome inhibitors have recently emerged as a new class of therapeutic agents that are effective in the treatment of several malignancies. The ubiquitin-proteasome pathway is critical for maintaining the intracellular milieu of cells by eliminating substrates that are involved in cell cycle regulation, survival, and apoptosis. Bortezomib is the first agent of this class that has also shown impressive activity in T-cell lymphomas and CTCL. A phase II trial of bortezomib carried out in multiple relapsed patients with CTCL showed an impressive RR of 67% in a cohort of 15 patients with 2 CRs (17%) and 6 PRs (50%). The responses were durable, lasting from 7 to 14 months. The cohort included 2 patients with PTCL, out of which 1 demonstrated a response. The main toxicity is neutropenia, fatigue, asthenia, and diarrhea.

**Conclusion**

At the present time, there are many promising therapeutic agents with activity against T-cell lymphomas. However, it is imperative that insight into T-cell lymphomagenesis will help guide the development of these agents so that targeted therapies can be developed for more effective clinical benefits. Major challenges still persist in this field, including (1) the optimal agents and strategy for combination therapies, and (2) the best strategy to accrue patients to clinical trials in this rare and heterogeneous group of diseases. Implementing well-designed multicenter clinical trials with careful thought to correlative studies will help answer some of the ques-
tions in this field. The goal remains to cure these diseases, and to change the treatment paradigms to more targeted and tailored approaches to individual tumors in patients with cancer.

Disclosures

Jasmine Zain has served as a member of the Speaker’s Bureau for Allos Therapeutics, Inc. Owen A. O’Connor has received research funding from Allos Therapeutics, Inc., Eli Lilly and Company, Merck & Co., Inc., Spectrum Pharmaceuticals, Inc.; and has acted in a consultant/advisory role for Allos Therapeutics, Inc.

References


The United States Cutaneous Lymphoma Consortium (USCLC)

Elise A. Olsen

There has been tremendous progress over the past 20 years in the area of cutaneous lymphoma. We now have a better understanding of lymphocyte biology as it pertains to the skin and therapeutic options that have moved beyond systemic chemotherapy for both cutaneous T-cell lymphoma (CTCL) and B-cell lymphomas. Updated staging and classification systems for both T-cell and B-cell cutaneous lymphomas have recently been published, and a consensus paper regarding new endpoints and response criteria for mycosis fungoides and Sézary Syndrome is being finalized. Together, these publications will allow standardization of clinical trials in cutaneous lymphoma regardless of what site in the world they are being conducted.

Much of the progress in the clinical care of patients with cutaneous lymphoma is directly related to the organizations arranged around these diseases such as the International Society for Cutaneous Lymphomas (ISCL), the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer (EORTC), and national organizations in various European countries and Japan. Recognizing a deficiency of information on the specifics of cutaneous lymphoma in the United States and the advantages of forming a national collaborative network for research in this area, a group of physicians first met in Buenos Aires, Argentina, on September 30, 2007, at the World Congress of Dermatology to plan a US organization to approach these objectives. The co-chairs of this meeting were Elise Olsen (Duke University) and Madeleine Duvic (MD Anderson). Others in attendance at this founding meeting were Tom Anderson (University of Michigan), Marie-France Demierre (Boston University), Larisa Geskin (University of Pittsburgh), Jakki Junkins-Hopkins (University of Pennsylvania), Joan Guitart (Northwestern University), Ellen Kim (University of Pennsylvania), Youn Kim (Stanford University), Stuart Lessin (Fox Chase Cancer Center), Pierluigi Porcu (Ohio State University), Sunil Reddy (Stanford University), Michael Tharp (Rush Medical Center) and John Zic (Vanderbilt University). The United States Cutaneous Lymphoma Consortium (USCLC) was thus formed with these specific goals: (1) creating a national registry of patients with cutaneous lymphomas; (2) developing and participating in cooperative clinical trials of cutaneous lymphomas and/or other collaborative/cooperative research projects; (3) developing guidelines of therapy for cutaneous lymphomas; and (4) developing a national tissue bank for cutaneous lymphomas.

The first election of directors of the USCLC was held in December 2008, and the first election of officers was held in March 2009 (Figure 1). This Board of Directors includes representatives from across the United States and from the fields of Dermatology, Oncology, Radiation Oncology, and Dermatopathology in keeping with the multidisciplinary nature of the society. Since March 2009, the USCLC has been able to accomplish the following on its way to becoming an active and productive group: (1) filed for and received 501-status as a nonprofit group; (2) created a committee structure to encourage multidisciplinary participation; (3) developed a plan for a national registry and financial support to initiate the process; (4) contracted for development of a website; (5) partnered with the ISCL on a World Congress of Dermatology to be held in Chicago in 2010. The organizational structure of the USCLC is as shown in Figure 1.

The creation of the USCLC should enable advancement in our knowledge of cutaneous lymphomas and those conditions that may lead to cutaneous lymphomas, and improve our outcomes from therapeutic interventions. Our overriding objective is to improve patient care. We believe that this multidisciplinary cross-pollination and active collaboration with other cutaneous lymphoma physician organizations, and the patient advocacy group Cutaneous Lymphoma Foundation, will help to meet this goal.

Disclosures
The author has no relevant relationships to disclose.

References

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Clinical Trials in Cutaneous Lymphoma

A Cutaneous T-Cell Lymphoma EORTC Trials Platform

Sean Whittaker

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Keywords: CTCL, Cutaneous Lymphoma Task Force, International cooperative group, Strategic development

Introduction

Cutaneous T-cell lymphoma (CTCL) is a rare disease with an incidence rate of 0.5-1.0 per 100,000. Although there are a large number of emerging novel therapies for CTCL, trials have been usually small and uncontrolled with most studies using response rates (RRs) as the primary endpoint. For some patients, CTCL is indolent and chronic, and the standard of care for early-stage disease is skin-directed therapy. However, there are no defined standards of care for advanced stages of the disease, which has a poor prognosis of 20%-50% 5-year survivals. There is a need for large coordinated clinical research trials for CTCL, especially for patients with intermediate to advanced stages of the disease, and those with refractory/recurrent disease. Because of the low incidence of CTCL, any study of this disease would need to establish broad international cooperation with an inclusive network of experts having complementary areas of expertise including dermatologists, pathologists, and oncologists.

The Setting: A Rare Tumor and an Unmet Need

Cutaneous T-cell lymphoma is a rare tumor, and there is an unmet need with respect to treatment as most therapies are associated with RRs of 30%-35%. Furthermore, though chemotherapy regimens tend to have higher RRs, the duration of response is often very short-lived. Therefore, the European Organization for Research and Treatment of Cancer (EORTC) Early Project Optimization Department (EPOD) coordinated efforts to support the Cutaneous Lymphoma Task Force in developing and implementing a trial platform in advanced disease that would define a set of clinical trials with critically relevant endpoints and strong translational research components, which lead to improved standards of care for CTCL.

The EORTC CTCL trials platform was the result of this effort and consists of 3 studies. The first is geared toward chemotherapy-naive patients, with advanced disease addressing maintenance of response. The second is a study designed to investigate whether a rational combination of novel biologic treatment agents could overcome resistance or increase efficacy in chemotherapy-resistant patients. The final study is for advanced-stage patients, to address the role of high-dose therapy and reduced-intensity allograft stem cell transplantation (RICalloSCT).

The Process: Developing the EORTC Cutaneous T-Cell Lymphoma European Platform

The EORTC Cutaneous Lymphoma Task Force is in a unique position to federate European and international research efforts to recruit patients, and can rely on the expertise of the EORTC headquarters in clinical trial operations and methodology. The EORTC Cutaneous Lymphoma Task Force worked closely with EPOD at all stages of project development, and in September 2007, discussions with Dr. Sean Whittaker (Chair), Dr. Robert Knobler (past Chair), and Dr. Martine Bagot (Chair-elect) resulted in the development of a group strategy. In January 2008, a strategy meeting was organized to gather experts in CTCL in order to reach a consensus on a master plan. A protocol development group was formed, and outlines developed.

The EPOD facilitated extensive discussions with industry and pharmaceutical partnerships followed. Partnerships were formed with the Celgene Corporation for the maintenance study, Merck and Johnson & Johnson Services, Inc. for the study investigating novel biologic combinations, and the European Group for Bone Marrow Transplantation (EBMT) and THERAKOS, Inc. for the RICalloSCT study. The EPOD also facilitated contacts and discussions with international cooperative groups such as the National Cancer Institute of the United States. In September 2008, the EORTC CTCL Trials Platform was launched.

The Outcome

Within the EORTC CTCL Trials Platform, the phase III EORTC 21081 trial will focus on chemotherapy-naive patients...
Figure 1: EORTC Clinical Trials Platform for Chemotherapy Naive Patients With Stages IIB-IV Cutaneous T-Cell Lymphoma

- **Debulking Therapy:**
  - Gemcitabine or Pegylated Liposomal Doxorubicin ± Radiotherapy

- **Randomization**
  - Patients with CR/PR
    - Debulking Therapy:
      - Gemcitabine or Pegylated Liposomal Doxorubicin ± Radiotherapy

- **Endpoint:**
  - PFS

- **Secondary Endpoint:**
  - OS

- **Outcome**
  - Observation

- **Eligible for Trial 21082**
  - Relapsed/Progressive Disease
    - Lenalidomide

- **Follow-Up**
  - Maintain Response

- **Other Therapy ± Radiation Therapy (Institutional Decision)**
  - Eligible for EBMT Trial

- **Patients with SD/PD**
  - Eligible for Trial 21082

- **Abbreviations:**
  - CR = complete response
  - EBMT = European Group for Bone Marrow Transplantation
  - EORTC = European Organization for Research and Treatment of Cancer
  - OS = overall survival
  - PD = progressive disease
  - PFS = progression-free survival
  - PR = partial response
  - SD = stable disease

Figure 2: EORTC Clinical Trials Platform for Refractory Stages IIB-IV Cutaneous T-Cell Lymphoma

- **Relapsed/Progressive/Refractory**
  - Trial 21082 Endpoints: PFS/OS

- **Randomization**
  - Single Arm:
    - HDACI (Vorinostat)
  - Combination Arm:
    - HDACI (Vorinostat) + Proteasome inhibitor (Bortezomib)

- **Outcome**
  - SDT Inappropriate
  - Progression

- **Other Therapy ± Radiation Therapy (Institutional Decision)**
  - Eligible for Trial 21082

- **Other Therapy ± Radiation Therapy (Institutional Decision)**
  - Eligible for Trial 3

- **Abbreviations:**
  - CR = complete response
  - EBMT = European Group for Bone Marrow Transplantation
  - EORTC = European Organization for Research and Treatment of Cancer
  - HDACI = histone deacetylase inhibitor
  - OS = overall survival
  - PFS = progression-free survival
  - PR = partial response
  - RISCT = reduced-intensity stem cell transplantation
  - SDT = skin-directed therapy
with advanced stages of (IIB-IV) of either mycosis fungoides (MF) or Sézary Syndrome (Figure 1). This trial will include patients who display advanced disease and those who have progressed from early-stage disease. The trial consists of debulking treatments (with either gemcitabine or liposomal doxorubicin single-agent chemotherapy and local radiation therapy, if needed) and addresses the question of whether it is possible to provide maintenance therapy that will improve progression-free survival (PFS). Following completion of debulking therapy, those patients with a complete or partial response are randomized to receive either lenalidomide (Revlimid™), or observation as maintenance therapy for up to a year. Lenalidomide is now licensed for the treatment of myelodysplastic syndrome and multiple myeloma (MM), and has been used experimentally in other lymphomas with promising results.

In patients with refractory/recurrent advanced stages (IIB-IV) of MF or Sézary Syndrome for whom first-line chemotherapy has failed, the phase III EORTC 21082 trial will compare PFS in patients receiving suberoylanilide hydroxamic acid (SAHA, Vorinostat™) in combination with bortezomib (Velcade®) to those receiving SAHA alone. Vorinostat is a potent inhibitor of histone deacetylase (HDAC) and received the Food and Drug Administration’s approval for CTCL in 2008. Bortezomib inhibits the 26S proteasome, and is licensed for MM (Figure 2). Bortezomib has shown activity in CTCL and other lymphomas including mantle cell lymphoma. There is emerging evidence suggesting synergy for Bortezomib and HDAC inhibitors, and clinical data on the safety of combined Bortezomib and SAHA.

Finally, there are ongoing discussions with the EBMT to establish a standard reduced-intensity conditioning allograft stem cell transplantation protocol for selected patients with advanced CTCL.

It is expected that this trial’s platform will use emerging International Society for Cutaneous Lymphomas EORTC consensus criteria for assessment of all 3 tumor compartments in CTCL (skin, node, and blood) to provide a consistent measure of treatment response in a global score. An extensive series of translational studies are planned to support this platform with the aim of (1) identifying the potential mechanisms of action of these therapies, and (2) predicting responders. These translational studies will use Luminex® platforms to analyze the modulation of cellular immune responses and cytokine/chemokine expression, transcriptome analysis of dysregulated signaling pathways in CTCL, and also create a tumor biobank.

Coordinated Strategic Project Development

The EORTC CTCL trials platform is a paradigm for the strategic development of EORTC trials required to address clinical issues in rare cancers. It is hoped that this will be accepted by licensing authorities, and will prove to be an acceptable strategy for partnerships with pharmaceutical companies.
Immune Modulators as Therapeutic Agents for Cutaneous T-Cell Lymphoma

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Keywords: Bexarotene, CTCL, Drug approval, Interferon, Vorinostat

Introduction

Cutaneous T-cell lymphoma (CTCL) at all stages appears to be responsive to immune-modulatory therapeutic approaches. Herein, we describe the mechanistic rationale for the use of interferons, interleukin (IL)-12, retinoids, Toll-like receptor (TLR) agonists, photopheresis, and combinations of immune-preserving, immune-stimulatory therapies for CTCL.

Significant immune dysregulation characterizes the progression of CTCL.1 Substantial recent evidence indicates that soluble factors released by the malignant T-cell population may play an important role in the pathogenesis of the immune abnormalities. Increased production of T-helper 2 (Th2) cytokines, including IL-4, IL-5, and IL-10, has been observed, and increased numbers of circulating regulatory T cells producing transforming growth factor-β have been documented among some patients with Sézary syndrome (SS).2 The end result of this is the depressed functions of multiple arms of the cellular immune response, including decreased numbers and functions of circulating dendritic cells and decreased numbers of cytotoxic T cells and natural killer (NK) cells. All of these cell types are critical for the mounting of an adequate antitumor immune response.

Despite a declining cellular immune response in association with progressing CTCL, preservation of the host immune response, along with the use of immune-modulatory therapy, remains an important treatment approach leading to significant clinical benefit, even for those with advanced CTCL. Moreover, patients with early-stage disease are particularly responsive to immune-modulatory therapy.

In choosing the ideal immune modulator, a number of factors should be considered. First, the agent should have the capacity to induce a robust antitumor immune response. The treatment should also directly produce high levels of apoptosis of the tumor cells. Finally, the ability to produce sustained immunologic memory against the tumor cells is of critical importance in an effort to produce prolonged clinical responses.

A number of cytokines that are products of cells of the innate immune system, including interferon (IFN)-α, IFN-γ, and IL-12, meet at least 2 of the above criteria with IFN-α meeting all 3. IFN-α has been shown to produce high clinical response rates in some studies.3 It is clinically effective as a single agent for all stages of disease, with perhaps lower response rates among patients with large-cell transformation or visceral disease. IFN-α has multiple beneficial effects on the host immune response, including activation of CD8+ T cells and NK cells, which are both putatively responsible for mediating direct antitumor cytotoxicity. IFN-α also directly inhibits proliferation of the malignant T cells in vitro and induces apoptosis of the malignant cells. Because IFN-α can activate CD8+ T cells, it should be used with caution for patients with CD8+ CTCL.

Both recombinant IFN-α as well as pegylated forms of IFN-α, which has the advantage of a much longer half-life, have been successfully used for the treatment of patients with CTCL.4 In low doses, the adverse effects of therapy are generally well tolerated, though the elderly tolerate IFN-α less well than do younger individuals.

Interferon-γ, a product largely of NK cells as well as CD8+ T cells, is also a valuable therapeutic agent for CTCL.5,6 It too activates cytotoxic cells, but it also has the added effect of enhancing macrophage and dendritic cell activity. The ability to prime dendritic cells should be an important property for patients receiving photopheresis. IFN-γ can enhance the ability of antigen-presenting cells to process the large numbers of apoptotic tumor cells that are generated as a result of the treatment. Moreover, IFN-γ can potently prime antigen-presenting cells to enhance IL-12 produc-
Immune Modulators in CTCL

### Table 1  Immune-Modulatory and Biologic Therapies for Cutaneous T-Cell Lymphoma

<table>
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Abbreviations: GM-CSF = granulocyte-macrophage colony-stimulating factor; TLR = Toll-like receptor.

...tion, which can further support a T-helper 1 (Th1) response, which is critical for optimal antitumor immunity.7

Interferon-γ also appears to be quite useful for patients with folliculotropic mycosis fungoides, particularly when it is combined with the topical TLR agonist imiquimod (AH Rook, unpublished observations). IFN-γ appears to synergize with multiple different TLR agonists in its ability to stimulate IL-12 production.8 This has been shown in vitro using the peripheral blood cells of patients with SS.7

A distinct advantage that IFN-γ possesses over IFN-α is a lower frequency of adverse effects on the cognitive abilities of the elderly. IFN-γ may also less frequently cause or aggravate depression in comparison with IFN-α.

Interleukin-12, a product of myeloid dendritic cells and monocytes, is another cytokine that has been demonstrated in phase I and phase II clinical trials to provide clinical benefit for patients with CTCL.9,10 As IL-12 does not directly inhibit the growth of malignant CD4+ T cells of patients with SS, it presumably mediates its beneficial effect through the enhancement of cytotoxic T-cell and NK cell activities and through the induction of IFN-γ by NK cells. Direct infiltration of regressing CTCL lesions with cytotoxic T cells with concomitant tumor cell apoptosis has been observed during IL-12 therapy.9 The phenomenon of cytotoxic T-cell infiltration within CTCL skin lesions has also been observed in a recent clinical trial using IFN-γ (AH Rook, unpublished observations). This likely is also an effect of IFN-α. Thus, the ability of each of these cytokines to activate and to mediate cytotoxic T-cell responses is of critical importance. As our patients with advanced-stage disease who appear to have the most sustained clinical responses to therapy have typically received an immune-potentiating cytokine in the interferon family, this should be advocated for such patients as first-line therapy.

Interleukin-21 is another immune-potentiating cytokine that is currently in clinical development for the treatment of a number of malignancies, including metastatic melanoma, for which clinical activity has been observed. It has the ability to potently activate NK cells and CD8+ T cells. Recent studies have demonstrated that IL-21 can enhance the immunologic functions of both NK cells and CD8+ T cells derived from the peripheral blood of patients with SS.11 Moreover, IL-21 can augment the ability of immune cells from these patients to directly kill malignant T cells in vitro. These in vitro observations, along with the clinical trial results for metastatic melanoma, suggest that IL-21 would likely be an active therapeutic agent for CTCL.

Systemic retinoids also represent a desirable first-line therapeutic choice for CTCL as they are therapeutically active and do not blunt the immune response. Bexarotene, which produces response rates approaching 50% for both early- and late-stage CTCL, has the ability to induce tumor cell apoptosis and to inhibit IL-4 secretion from the patients’ T lymphocytes.12 Bexarotene also appears to inhibit expression on the malignant T cells of certain chemokine receptors, particularly CCR4, that are critical for permitting the cells to gain access to the skin.13 In concert with the inhibition of expression of CCR4 is the blunting of chemotaxis of the bexarotene-treated malignant T cells in response to the chemokine TARC (CCL17), which is the epidermal-derived ligand for CCR4.13 Thus, bexarotene appears to exert multiple beneficial effects in the therapy of CTCL.

It is noteworthy, however, that some patients can become resistant to bexarotene therapy. We have identified among some bexarotene-treated patients the subsequent outgrowth of circulating malignant T-cell clones that lack RXR receptors, which may preclude the binding and proapoptotic effects of bexarotene.14 Although these patients were clearly sensitive to therapy at the outset, with bexarotene manifesting proapoptotic effects on their malignant T cells, they ultimately manifested disease progression in association with in vitro resistance of the their malignant T cells to bexarotene-induced apoptosis (AH Rook, unpublished observations).

The findings of bexarotene resistance represent an important basis for using multimodality immune-based regimens in an effort to target the malignant T cells with agents that exert different mechanisms of action of tumor cell killing. Thus, we frequently combine bexarotene with an interferon or with photopheresis, or both, particularly for patients with leukemic variants of CTCL. Bexarotene can also be a useful therapeutic adjunct for patients receiving phototherapy. Combining interferons with phototherapy can also represent a useful approach with an increased rate of therapeutic efficacy.

There is also emerging evidence that TLR agonists represent a class of therapeutic agents that may prove to be highly effective for CTCL, even among those with advanced-stage disease.15 It has long been known that topical imiquimod, a TLR7 agonist, has the ability to activate the local cutaneous immune response in and around malignant lesions, resulting in the regression of CTCL patches and plaques.10 Responses may be quite variable based upon the low bioavailability of imiquimod. Some patients may have quite low numbers of TLR7-expressing cutaneous plasmacytoid dendritic cells, particularly if they have recently used skin-directed therapies that may diminish numbers of these cells, including topical steroids, psoralen and ultraviolet A (PUVA), or radiation therapy. Resiquimod, which is under clinical development, has a much higher level of bioavailability and thus may produce substantially higher response rates than imiquimod. Furthermore, resiquimod triggers TLR8 in addition to TLR7. The ability to trigger TLR8 carries the advantage of the potential to activate myeloid dendritic cells, which are potent producers of IL-12.
Clinical trials have begun with parenterally administered TLR agonists. Recently, a phase I trial using a type B CpG, which triggers plasmacytoid dendritic cells that bear TLR9, demonstrated efficacy among patients who were highly pretreated and refractory to multiple therapies. Several patients in the trial with advanced-stage CTCL refractory to multiple systemic therapies experienced complete clinical responses. Moreover, we have demonstrated that CpGs in vitro can potently activate NK cells and cytotoxic T cells of patients with SS. Thus, since CpGs can activate cytotoxic T cells, leading to an enhanced antigen-specific cytotoxic T-cell response, this family of compounds is likely to represent an active additional component of a multimodality immune-modulatory approach.

In this regard, CpGs and other TLR agonists are likely to augment the response rates achieved with extracorporeal photopheresis. Our center has found photopheresis to be particularly useful for patients with leukemic involvement. Although photopheresis may be used as monotherapy, it is important to stress that multiple groups have observed higher response rates when photopheresis was combined with immune adjuvant agents such as interferons, retinoids, or granulocyte-macrophage colony-stimulating factor. Toll-like receptor agonists have not yet been tested with photopheresis. Nevertheless, activation of antigen-presenting cells (APCs) by TLR agonists would likely represent a beneficial effect because APC processing of the photopheresis-treated T cells is a critical part of the efferent response to photopheresis. Moreover, as described above, TLR agonists are powerful activators of what would be considered the efferent response to photopheresis, specifically the activation of NK cells and cytotoxic T cells, both of which can lyse malignant T cells. Thus, clinical trials of TLR agonists with photopheresis for leukemic variants of CTCL should be considered highly desirable.

Photopheresis used in combination with other immune-augmenting agents has resulted in clinical remission in nearly 30% of our patients with SS along with partial responses among another 50%. These high response rates should suggest a bright future for the continued development of new immune-modulatory agents. Our therapeutic “wish list” presently includes IL-12, IL-21, and TLR agonists (Table 1). Other novel approaches that harness the immune response should include anti–T-cell vaccination and efforts to develop targeted therapeutic agents that preserve the host immune response. Much work remains to be accomplished.

Disclosures
The authors have no relevant relationships to disclose.

References
Clinical Trials in Cutaneous Lymphoma

Hematopoietic Stem Cell Transplantation for Cutaneous T-Cell Lymphoma

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Introduction

Cutaneous T-cell lymphomas (CTCLs) are rare disorders that typically have a good prognosis.1-4 Mycosis fungoides (MF), the most common CTCL, usually presents in early stage with scaly patches and plaques. Management most often involves topical skin-directed therapy, and the prognosis is typically excellent. However, once tumor stage progresses, or nodal or visceral disease develop, or once patients develop Sézary syndrome (SS) or large-cell transformation, the overall prognosis is generally poor, and most patients do not survive beyond 5 years.2 While new therapies have become available for patients with advanced CTCL, most treatments remain palliative, and prolonged remissions or cures are rare. For some of these patients, high-dose chemotherapy or chemoradiation therapy followed by either autologous or allogeneic stem cell transplantation has been attempted in order to increase the rate of response and prolong overall remission duration.5 Herein, we discuss the most recent data regarding transplantation-based approaches for advanced CTCL.

What Is the Role for High-Dose Chemotherapy and Autologous Hematopoietic Cell Transplantation in Mycosis Fungoides and Sézary Syndrome?

Currently, there are fewer than 10 published manuscripts in the English-language literature that report outcomes in patients with advanced CTCL having undergone autologous blood or marrow cell transplantation.3,6-12 These reports contain from 1 to 8 patients each, with a median of only 1 patient per report. Bone marrow was the source of engrafting cells in most of the older reports, but more recently, peripheral blood has been the predominant source of reconstituting cells. Interestingly, some of the autografts were T-cell depleted, with investigators reasoning that ex-vivo T-cell depletion would limit the risk of relapse by removing contaminating malignant cells.5,11 Collectively, 20 patients have been reported using 8 different conditioning regimens. To summarize, autografts for advanced MF and SS have been associated with low treatment-related mortality rates and achievement of initial complete remission (CR) in the majority of patients. However, remissions have generally been of short duration, and the median time to progression has been roughly 2-3 months. Overall, the 1-year progression-free survival (PFS) has been less than 20%. Anecdotally, some patients seem to experience relapse following autologous transplantation with a form of disease that behaves in a more indolent fashion and may be more responsive to interventions than before transplantation.5 There is no formal proof that this is indeed the case. Nevertheless, the overall results with high-dose therapy and autologous transplantation are not all that encouraging and do not seem to represent a clear advantage compared other more conventional and potentially less toxic approaches. Thus, it is difficult to recommend autologous transplantation for most patients with advanced CTCL outside the context of a clinical trial evaluating some novel approach such as maintenance therapy after autograft.

What Is the Role for Allografting?

It is difficult to know when and if allogeneic transplantation should be considered in patients with advanced CTCL. Historically, given the potential toxicities related to the conditioning regimen and graft-versus-host disease (GVHD), it has been a consideration for only a very small subset of younger patients without significant comorbidities. Given the small numbers of patients who would be candidates for traditional myeloablative allografting, most large cancer centers have not expended the effort to evaluate allogeneic transplantation for CTCL in a prospective manner. However, with the advent of reduced-intensity conditioning (RIC)-based approaches to allogeneic transplantation over the past decade, and the successful application of RIC allografting in other lymphoid malignancies, there is now the opportunity to reconsider the option of allografting for older patients with CTCL, even those with a number of other medical conditions that previously may have contraindicated traditional myeloablative allografting.5 Whether there will ever be enough patients to determine in what settings allografting is superior to other available therapies for CTCL remains an open question. To date, the
majority of patients who have undergone allografting for CTCL are those for whom multiple alternative therapies have failed and allografting therefore seemed worth the risk.

It is important to note that the general considerations that apply to all patients potentially eligible for allogeneic stem cell transplantation apply to those with advanced CTCL. These include, first and foremost, the identification of a suitable donor and knowing what constitutes a suitable donor (eg, related, unrelated, umbilical cord blood). An assessment of the individual patients' risk for complications, including regimen-related toxicity, graft failure, acute and chronic GVHD, opportunistic infection, and relapse, are essential to make the appropriate choice of conditioning regimen (reduced intensity vs. myeloablative) and supportive care (eg, choice of GVHD prophylaxis).

Current trends in allografting for patients with T-cell lymphoma in general are changing, as recent data suggest that more patients are actually being referred and undergoing transplantation compared with previously. Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) covering the years 2002-2007 reveal an approximate 38% increase in the number of patients undergoing allografting for any type of T-cell lymphoma (Marcel Pasquini, unpublished data). Most of these patients have received RIC allografts, and peripheral T-cell lymphoma and angioimmunoblastic lymphoma make up the histology of the majority of patients undergoing transplantation. Large cancer cooperative groups have initiated or are planning prospective trials given the unmet needs in this area. It is this general interest in the application of RIC allografting for T-cell lymphomas, attempting to capitalize on the putative graft-versus-lymphoma (GVL) effect, that continues to drive interest in its application in selected patients with CTCL.

Before 2010, there were about 8 published articles in the English-language literature detailing outcomes of patients undergoing allografting for advanced CTCL.9,13-19 Of the 21 patients reported before 2010, most had undergone transplantation with stage IIB-IV disease or advanced SS. Seven different conditioning regimens were used in these earlier reports. Sixteen of the patients received matched sibling allografts and 5 transplants from volunteer unrelated donors.

The largest experience published in the peer-reviewed literature before 2010 was reported by Molina and colleagues from the City of Hope.18 They reported on 8 patients with advanced MF/SS who received allografts from 1996 to 2002. These patients had received a median of 7 previous therapies (range, 5-12 therapies). Four received myeloablative conditioning, and 4 received RIC. Half received transplants from matched sibling donors, and the other 4 received transplants from matched unrelated donors. The patients had a median age of 45 years (range, 21-59 years). All achieved a CR within 30-60 days following transplantation, confirmed by polymerase chain reaction (PCR) analysis of peripheral blood and bone marrow in the majority of the patients. Twenty-five percent of the patients died of treatment-related mortality, and 6 were alive in remission at a median follow-up of 56 months (range, 33-108 months). Of 4 recipients of RIC, 3 were alive and in remission at the time of the report. Interestingly, most patients in remission had some evidence of chronic GVHD.

Duarte and colleagues presented a retrospective analysis in abstract form from the European Blood and Marrow Transplant Group (EBMT) of 64 patients with advanced CTCL who received allogeneic transplants between 1997 and 2006.20 A total of 23 of these patients had MF, 21 had SS, 16 had primary cutaneous anaplastic large-cell lymphoma, and 4 had subcutaneous panniculitis-like lymphoma. The median age was 46 years (range, 5-65 years). There were 38 men and 26 women. The median follow-up of survivors was 28 months. The median number of previous therapies was 3 (range, 1-8 therapies). Stem cell source was peripheral blood in 54 patients and bone marrow in 10 patients. The majority (n = 52) received transplants from matched related donors, and 12 received transplants from unrelated donors. Sixty-four percent of the patients received RIC before transplantation. At the time of transplantation, about half had relatively refractory disease, 23% were in CR, and 26% were in partial remission. The remaining patients had primary refractory disease and were not in remission at the time of transplantation. The overall nonrelapse mortality rate at 3 years was 24%; this rate was 16% in the reduced-intensity group and 35% in the conventional-intensity group. Acute GVHD occurred in 37%, and chronic GVHD occurred in 69%. The relapse rate was 36% overall; the relapse rate was only 21% for those in remission versus 46% for those not responding. The overall PFS rate was 41%; this rate was 58% for patients in remission versus 26% for those with refractory disease. Of note, there was no significant difference in the risk of relapse or PFS comparing recipients of reduced-intensity versus conventional myeloablative conditioning. Overall survival (OS) was 55% at 3 years and was 65% for those in remission versus 46% for those not in remission.

A recent meta-analysis compared allografting versus autografting for advanced CTCL. The authors reviewed essentially all of the published literature, detailing outcomes in 19 autologous and 20 allogeneic recipients. They generated Kaplan-Meier curves for both event-free survival (EFS) and OS and found significant differences in favor of allogeneic transplantation for both EFS and OS. Nevertheless, it is difficult to reach any firm conclusions based on this report because it involved only 39 patients who underwent transplantation over a prolonged period of time using multiple conditioning regimens, heterogeneous supportive care, and wide variety of donors. There is certainly a hint that allografting may be advantageous, at least for a subset of patients with advanced CTCL, given the possible GVL effect that reduced the risk of relapse.21

In summary, very few patients undergoing allografting for advanced MF/SS have been reported in the literature. Until recently, most of the data have been retrospective, and most of the patients undergoing transplantation have been younger and are likely to represent a highly selected group. In addition, there is the possibility of a publication bias in favor of reporting good outcomes. The number of failed allografts for CTCL that have not been reported cannot be known for certain, although it is likely to be a small number. Notwithstanding, encouraging PFS and OS rates have been reported following allogeneic transplantation, particularly following RIC, and suggest a putative GVL effect. Prospective trials appear warranted, but are they feasible?

**Is a Prospective Clinical Trial of Allografting for Advanced Cutaneous T-Cell Lymphoma Feasible?**

For those who treat patients with advanced CTCL, this is becoming a relevant question. In constructing such a trial, there are a number of important considerations. What should constitute the eligibility
criteria? What is the most relevant primary endpoint: response rate or PFS? If PFS, what would be an encouraging 2-year PFS rate? What is an acceptable risk of nonrelapse mortality? Should such a trial include only an RIC allografting approach or should more intensive regimens be explored? How should we choose among the several available regimens? Should such a study include both matched sibling and volunteer unrelated donors? How many patients would be required to complete a phase II study? The answer to this last question would depend on the endpoint chosen, but probably at least 40-50 patients would be required. If so, are there enough patients to complete such a trial in a timely fashion for the study results to remain relevant? The report from the EBMT involved 64 for patients who underwent transplantation from 1997 to 2006. Unofficially, the CIBMTR registered approximately 40 patients in the past 5 years (Marcelo Pasquini, unpublished results). Overall, it seems unlikely that more than 20 allografts are performed annually for this diagnosis worldwide.

Undaunted by these numbers, the MD Anderson Cancer Center (MDACC) embarked on a single-center prospective study evaluating an RIC regimen with fludarabine and melphalan following total-skin electron beam radiation. A total of 19 patients with advanced CTCL with a median age 50 years (range, 21-63 years) and a median of 4 previous therapies underwent transplantation using stem cells from related or unrelated donors. The 2-year OS was 79%, with a 2-year PFS of 53%. The risk of nonrelapse mortality was only 12% at 2 years. Interestingly, some patients relapsing after allograft achieved remission after withdrawal of immunosuppression with or without the addition of other therapies, suggesting once again the existence of a GVL effect that may take more than 2-3 months to develop. These encouraging results in a group of patients with relatively refractory disease demonstrate the promise and efficacy of this approach for selected patients. Another prospective trial is ongoing at Stanford University evaluating total lymphoid irradiation and antithymocyte globulin-based conditioning with a primary endpoint of EFS. This trial was opened in May 2009 and has an accrual goal of 40 patients (NCT00896493). It will be interesting to see if this goal can be met, particularly because the MDACC took 7 years to accrue 19 patients.

At any rate, the data that have been reported to date using allogeneic blood cell transplantation following RIC allografting is sufficiently interesting to pursue in patients with high-risk disease with few less-toxic alternatives. Some scientific questions to consider include identification of the target antigens of the GVL effect and how this effect can be augmented. Could donors be immunized to augment GVL because tumor tissue is accessible? How should patients be monitored after allografting for signs of minimal residual disease (eg, PCR methodology). Future prospective trials should attempt to address these and other questions.

**Conclusion**

How should we proceed when considering a patient with advanced CTCL for transplantation in the absence of a prospective clinical trial? Should decisions be made on a case-by-case basis? Here, the transplantation physicians will continue to rely heavily on the judgment of the physicians caring for patients with CTCL on a daily basis. Clearly, we should try to develop consensus among treating physicians at a national level if at all possible and certainly within individual centers. We should choose approaches that attempt to exploit the GVL effect while avoiding as much as possible the toxicity of intensive conditioning. Patients deemed eligible should be considered for both matched sibling and unrelated donor transplantation, and we should allow these patients to be enrolled in other clinical trials asking transplantation-related questions until we are able to generate interest in multicenter prospective trials.

**Disclosures**

The author has no relevant relationships to disclose.

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Radiation Therapy and Cutaneous Lymphoma

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Introduction

Cutaneous lymphomas are typically present with either a T-cell or B-cell phenotype and comprise approximately 5%-10% of all non-Hodgkin lymphomas. Compared with the nodal lymphoma literature, there is relatively little published on the cutaneous lymphomas and even less on appropriate therapeutic interventions. According to the National Cancer Institute’s Surveillance, Epidemiology, and End Results program, as of 2001, the incidence of mycosis fungoides (MF), which is the most common type of cutaneous T-cell lymphoma (CTCL), was approximately 5 per 1 million persons in the United States. The incidence of cutaneous B-cell lymphomas appears to be increasing and is slightly lower than CTCL, with approximately 3.5 cases per 1 million persons. Prognosis for patients with CTCLs is dependent upon the degree of cutaneous involvement and cell type, and the same holds true for the cutaneous B-cell lymphomas. It is notable that with regard to cutaneous B-cell lymphoma for example, diffuse large-cell lymphoma (DLBCL), leg type, is more aggressive than other histologies in other locations. It should be remembered that although MF is the most common cutaneous T-cell lymphoma, there are a variety of other cell types that have various clinical presentations and prognoses. Management strategies can differ widely, depending on the cell type, stage, and clinical presentation.

Cutaneous T-Cell Lymphoma–Mycosis Fungoides

As MF is the most common T-cell lymphoma, most of the studies published regarding radiation therapy have incorporated treatment results for this subtype. Unilesional disease or several lesions that can be encompassed in either 1 radiation therapy port or several small ports are typically treated with 2-3 cm of border and fractionation typically ranging from 1.5 to 2.5 Gy per day, with a total dose of 30-40 Gy. A more complicated technique, which is often used in widespread patch-plaque MF, is total-skin electron beam radiation therapy (TSEBT). This treatment can be delivered in several different ways, but the Yale University School of Medicine treatment protocol calls for treatment delivery over approximately 9 weeks, 4 days per week. Six different treatment positions are used to unfold skin creases to provide the most appropriate distribution of dose to all skin surfaces (Figure 1). Radiation therapy is extremely effective, with response rates (RRs) of 100% and complete response (CR) rates in excess of 90% for patients with localized MF. Cotter et al reported results for a small group of patients with a minimum 1-year of follow-up. The local recurrence rate was nearly 50% for those managed with a dose ≤ 10 Gy, 32% for those managed with 10-20 Gy, and 21% for those receiving 20-30 Gy. For any patient who received a dose > 30 Gy, there was no local failure. In 1998, Wilson et al reviewed the clinical outcomes for 21 patients with a total of 30 lesions, all of whom had stage IA MF and were managed with radiation therapy alone. Median follow-up was 3 years with a median dose of 20 Gy, but 17 patients received a dose > 20 Gy. The CR rate was 97% with a local control rate of 75% at 5 years. Micaly et al published an approximately 85% 10-year relapse-free survival (RFS) rate for a group of 18 patients with unilesional MF treated with a dose of approximately 30 Gy. Based on these relatively small studies, it does appear that there is a dose response, and it is most appropriate to offer a dose of at least 30 Gy to patients with unilesional MF.

Total-skin electron beam radiation therapy is extremely complicated and is best offered by centers with experience in the technique because it is one of the most technically challenging therapies in all of radiation oncology. Basic guidelines regarding TSEBT and its delivery have been established by the European Organization for Research and Treatment of Cancer (EORTC). A review of both a single-field and dual gantry angle beam technique has been published by Chen et al. For patients with widespread patch-plaque disease, or patch-plaque with limited tumor disease, TSEBT offers excellent rates of local control and affords a higher RR than any other form of therapy. As established by the EORTC, there are basic guidelines that should be followed that will ensure appropriate dosimetry and uniformity of radiation delivery (Table 1). With any TSEBT program, there is a variety of shielding that takes place. For the eyes, a combination of external and internal eye shields is incorporated into the treatment protocol. Shielding of the fingernails, hands, toenails, feet, and in some cases, the lips, ears, and genitalia for a portion of the treatment are also an important consideration. It has been greatly debated as to whether TSEBT...
offers a survival benefit even for early-stage patients, but there is no question that it is successful in achieving remission for patients. It is an excellent palliative modality for those in need of such care. Side effects of TSEBT may include pruritus, epilation, desquamation, erythroderma, hyperpigmentation, lower extremity edema, bullae, decreased sweating, dryness of the skin, alopecia, and loss of nails. More chronically, effects such as atrophy of the skin, decreased sweating, alopecia, telangiectasias, tanning of the skin, and second dermatologic malignancy are possible.

Following a course of TSEBT, it is essential that all patients be considered for maintenance therapy. This can take many forms, but Quiros and colleagues evaluated the use of psoralen in addition to ultraviolet A light (PUVA) as adjuvant therapy for a group of patients treated at Yale, and the use of adjuvant PUVA appeared to provide significant benefit in terms of improvement in 5-year RFS compared with those who did not receive such therapy adjuvantly following TSEBT. In 1999, a Stanford group also published a series of patients with T2 disease, and this revealed potential
benefits for the use of mechlorethamine as adjuvant/maintenance therapy for patients. Adjuvant therapy should also be considered for patients with advanced stages of disease, and this may take various forms, including extracorporeal photopheresis, interferon-α, bexarotene, denileukin diftitox, and other targeted therapies and combinations of therapies.

For those in whom an initial course of TSEBT fails, repeat treatment can be considered, and there are published data reviewing the safety and results of such programs. Both Yale and Stanford universities have reviewed their repeat treatment experiences, and RRs to a repeat course nearly approach the RRs of the initial course. It must be kept in mind that fractionation is essential in attempting to avert acute and long-term toxicities of the skin, especially in the setting of repeat treatment. The most superior outcomes were found in patients who have longer disease-free intervals between the 2 courses, a CR following a first course, and diffuse cutaneous involvement at the time of relapse. Although survival may not be enhanced with a repeat course, many patients who are in need of palliation certainly can derive benefit.

Patients with erythrodermic MF (T4) often have significant pruritus and are extremely symptomatic. Although it can be challenging to clear these patients of their disease with any therapy or combination of therapies, TSEBT may have a role for these patients. Total-skin electron beam radiation therapy has also been safely combined with extracorporeal photopheresis for such patients, and there may be improvement in cause-specific survival.

Complete response rates for patients who receive TSEBT range from 30% to 90%, with the highest responses in those with minimal patch-plaque disease and lower RRs in those with severe erythroderma.

Another commonly encountered type of CTCL is CD30+ anaplastic large-cell lymphoma. There is extremely limited experience in the role of radiation therapy for this disease, but it does appear to be responsive to radiation therapy. In 2008, a Yale University group published a small series of 8 patients who received 40 Gy, all of whom had a CR to treatment. All patients were without evidence of disease at a median follow-up of 12 months. These patients generally have a favorable prognosis, but only patients with limited cutaneous disease are candidates for radiation therapy alone.

**Cutaneous B-Cell Lymphoma**

After appropriate evaluation and diagnosis/classification, consideration can be given to treatment of certain isolated lesions with radiation therapy alone or small groups of lesions that can be encompassed within 1 radiation therapy port. Typically, superficial electrons are used, and these lymphomas tend to be relatively low grade. They are extremely responsive to radiation therapy doses in the range of 30 to 40 Gy and fraction sizes of 1.5 to 2.0 Gy per day 5 days per week. Fields typically have 2-3 cm margins around the area of erythema, and the RR is typically 100%. In 2004, Smith et al published a retrospective series of 34 patients who had received between 20 and 48 Gy with a relapse rate of 38% and a 5-year overall survival of 96%. The relapse-free survival (RFS) was 55% at 5 years. This paper also endeavored to reconcile some of the issues between the EORTC’s and the World Health Organization’s (WHO) classification systems because, at the time, there was not 1 uniform system in existence. Of the 34 patients, biopsy material was adequate for classification in 32, and 17 of the patients (53%) were classified as having follicle center cell disease by EORTC and diffuse large cell by WHO (follicular center cell/DLBCL). A total of 8 patients (25%) were thought to have follicle center cell by the EORTC classification and follicular type by the WHO (follicular center cell/follicular). Thirteen percent of the patients were classified as having marginal zone lymphoma, and only 3 of the 32 patients (9%) were thought to have large B-cell lymphoma of the leg type by EORTC classification and DLBCL by the WHO criteria. The median dose of radiation therapy was 40 Gy, and electrons were used in 26 patients. As noted above, all patients had a CR. However, at 5 years, 21% of the patients did develop extracutaneous disease. Patients who received < 36 Gy did seem to be at an increased risk for local recurrence with a 5-year local RFS of 50% compared with 90% for those receiving ≥ 36 Gy. Age, sex, duration of symptoms, history of pseudolymphoma, race, the locations and number of lesions, size of the largest lesion, presence of documented B-cell clonality, radiation therapy field number, and systemic therapy use did not correlate with risk of recurrence.

Although a variety of modalities have been evaluated in the treatment of patients with B-cell lymphoma, it seems that radiation therapy, much like with CTCL, provides the highest RR.

One particular scenario that is more commonly seen is a patient who presents with multiple cutaneous B-cell lymphoma lesions that cannot be encompassed in a single radiation therapy port, or lesions that cover many zones of the body. Although there are limited data, rituximab may be useful in these situations because often these lesions, assuming they are CD20+, have excellent RRs to this systemic agent. It is unclear as to how many cycles should be incorporated in the management of such patients or for what duration. If there are small groups of lesions or a single lesion that appears to be recalcitrant to such treatment, certainly radiation therapy can be considered.

**Conclusion**

The management of cutaneous lymphoma provides for a great challenge given the wide variety of histologies, differences in clini-
cal behavior between the B-cell and T-cell lymphomas, and various stages of presentation. There are multiple therapeutic interventions available, but radiation therapy is extremely useful in the management of patients with both T-cell and B-cell lymphomas, provides the highest rate of CR compared with all other therapies, and can be used as a tool to achieve superb palliation in patients in need.

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**References**

Local Versus Systemic Treatment for Primary Cutaneous B-Cell Lymphoma

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Prognosis and Predictive Factors

The prognosis of primary cutaneous marginal zone B-cell lymphoma (PCMZL) is excellent, with exceedingly rare disease-related deaths at 5 and 10 years.1-6 Skin relapses are common. Large-cell transformation and systemic involvement are seen in a minority of patients. The clinical course of primary cutaneous follicle center lymphoma (PCFCL) is usually indolent, with 5-year disease-specific survival rates of approximately 95%. Similar to PCMZL, skin relapses are often witnessed during the course of the disease. Bone marrow involvement may be present in approximately 10% of patients at the time of diagnosis. Individuals with bone marrow involvement had a 5-year overall survival (OS) and disease-specific survival of 44% and 63%, respectively, compared with 84% and 95% for patients without marrow involvement. The prognosis of primary cutaneous large B-cell lymphoma, leg type (PCLBCL-LT), is the least favorable of all primary cutaneous B-cell lymphomas (PCBCLs). The disease-specific survival is approximately 50%, and half of the patients develop clinically documented extracutaneous disease. Willemze et al reported by univariate analysis that only age and extent of skin lesions were associated with a poorer outcome.1 The 5-year OS for patients with a solitary tumor was 70% compared with 27% and 0% for patients presenting with localized or multifocal disease, respectively.

Treatment

A recent publication from the International Society for Cutaneous Lymphoma/European Organization for Research and Treatment of Cancer highlights consensus recommendations for the management of PCBCL. This was a collaborative effort by an international team of dermatologists, pathologists, hematologists, and medical oncologists with significant expertise in the field. In a separate report by Zinzani et al addressing prognostic factors in PCBCL, it was noted that for PCMZL and PCFCL, a plateau in disease-free survival did not occur until 15 years7 and, for PCLBCL-LT, not until 10 years from diagnosis and treatment.8 Local radiation therapy (RT) is a well-known and effective treatment modality in the field of PCBCL. It is widely given to patients with indolent PCBCL with curative intent. In particular, RT is a safe and effective treatment for patients with PCMZL and PCFCL with solitary or localized skin lesions. Patients with multifocal skin disease showed a tendency toward higher relapse rate (PCMZL and PCFCL) and extracutaneous dissemination (PCFCL), suggesting that other treatment modalities might be considered in such patients. Moreover, for patients with PCFCL presenting with skin lesions on the leg and for patients with PCLBCL-LT, RT should not be the first choice of treatment. Major limitations in reviewing on the treatment of PCBCLs were that (1) there was a complete lack of systematic reviews and large (randomized) controlled trials; (2) information on relapse-free survival or progression-free survival was often not included; and (3) in many studies, follow-up was too short to draw conclusions on long-term efficacy.

Primary Cutaneous Marginal Zone B-Cell Lymphoma

Patients presenting with solitary or few scattered skin lesions should be treated with local RT (20-36 Gy) or surgical excision.2-3,7,9-21 Almost all treated patients achieve a complete remission; however, a cutaneous relapse will occur in about half of these patients. In patients with extensive skin lesions, a large spectrum of therapeutic options are considered acceptable, including oral chlorambucil, interferon (IFN)-α, rituximab, and other therapeutic agents used for indolent low-grade systemic non-Hodgkin lymphomas, including fludarabine-containing regimens and cladribine. Observation is an acceptable alternative in selected patients with multifocal disease. Prognosis of primary cutaneous marginal zone B-cell lymphoma, associated with Borrelia burgdorferi infection, should receive specific antibiotics, but limited efficacy data are available.22,23 Patients who experience transformation with a large-cell phenotype and extracutaneous manifestations should be treated as having diffuse large B-cell lymphoma (DLBCL).
Primary Cutaneous Follicle Center Lymphoma

Patients presenting with solitary or localized skin lesions should receive spot RT with a dose of at least 30 Gy and a margin of clinically uninvolved skin of at least 1 to 1.5 cm.2,7,9,24-32 Similar to PMZML, almost all patients will enter a complete remission; however, a cutaneous relapse will appear in half of the patients. Solitary lesions that are small and well demarcated can be treated with surgical excision. For patients presenting with generalized skin lesions, observation can be an acceptable alternative. Patients requesting intervention should be treated with IFN-α, single-agent rituximab, or rituximab combined with systemic chemotherapy; single-agent or combination drug regimens have been used. Regarding rituximab, it seems interesting to explore the long-term efficacy of this therapeutic agent in generalized PCFCL. Moreover, comparisons between systematic and intralesional treatments deserve further investigation. Also, in patients treated intralesionally, a complete disappearance of B cells in the peripheral blood has been noted, indicating a systemic effect.15,26 Thus, intralesional rituximab might prove to be an equally effective but much more cost-effective alternative for systemic rituximab in patients with PCFCL with extensive skin lesions. Patients who transform with a large-cell phenotype and extracutaneous manifestations should be treated as having an intermediate-grade lymphoma.

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

The general consensus is that PCLBL-LT has morphologic, phenotypic, and clinical behavior similar to that of a systemic DLBCL and should be treated in a comparable manner.2,7,9,33-40 There is debate on whether patients with solitary small lesions should receive RT alone. Reported relapse rates are around 60%, and a substantial number of these patients present relapse with systemic involvement. The value of rituximab combined with multiagent chemotherapy such as cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) with or without involved-field consolidation RT remains to be proven (though appealing, based on results with DLBCL). For younger patients with relapsed disease, autologous or allogeneic stem cell transplantation also play an important role, similarly to patients with DLBCL.

Controlled multicentre studies are also required to assess the efficacy of several other new therapies, such as intralesional IFN-α for indolent PCLBL,38,39 Yttrium-90 ibritumomab tiuxetan or 131I-tositumomab radioimmunotherapy,41 pegylated liposomal doxorubicin (plus rituximab),34 and gene therapy with adenovirus-mediated transfer of IFN-γ.35

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References

Multidisciplinary Care in the Management of Patients With Cutaneous Lymphoma: A Perspective

Youn H. Kim

Introduction

Organized teamwork is essential for quality and productive outcome of group activities, as is well demonstrated in team sport events. To have a successful baseball team, we need members with different skills. A competitive team cannot have all great pitchers or catchers, but rather, an ideal baseball team should have a balance of skilled pitchers, catchers, fast runners, runs batted in/home-run hitters, agile shortstops, and outfields who work synergistically and share the passion to bring the team to a winning experience. These general concepts apply to taking care of our patients with cancer, with the goal of ameliorating their disease and improving the quality of their lives. The important skill sets in the care of patients with cutaneous lymphoma includes expertise from the key clinical disciplines such as dermatology, medical oncology, radiation oncology, and pathology. The foundation for a successful multidisciplinary care is established when the clinical care providers from these disciplines are identified who share the same passion and goals. With effective teamwork and productive synergy, this multidisciplinary care team will yield the best management outcome for our patients with cutaneous lymphoma.

Key Elements in Establishing a Multidisciplinary Group

The 3 key elements for building a successful multidisciplinary group include critical mass of health care providers representing each discipline, teamwork, and synergy (Figure 1).

The essential clinical disciplines in the care of patients with cutaneous lymphoma are dermatology (cutaneous oncology), medical oncology, radiation oncology, and surgical pathology (dermatopathology). Integration of blood and marrow transplantation service is also important whenever possible because there is cumulative evidence for clinically meaningful graft-versus-lymphoma effect in mycosis fungoides and Sézary syndrome. Establishing channels of easy access and great working relations with experienced members in diagnostic radiology or surgical oncology is also essential. For our rare pediatric patients, identifying those collaborators in pediatric dermatology and pediatric oncology is important so that we can elicit their help when circumstances arise. There should be adequate number representation from each discipline to provide appropriate depth and critical mass in patient management. Thus, if medical oncologist A is out of town or otherwise unavailable, medical oncologist B can step in to maintain the continuity and quality of patient care.

Synergistic teamwork is the ideal group interaction. Individual work that is additive is not a failure of a group; however, when the member contribution mounts to a level that supersedes the sum of each components, it is the most ideal. Synergy is possible when team members with different expertise share the passion to accomplish the very best. Members with unique attributes and experience thus challenge and stimulate each other to think, perform, contribute, and be accountable to the greatest level.

Operational Models

There are 3 main operational models of multidisciplinary clinical care, each with different benefits and challenges.

Joint Clinic in One Physical Space

A multidisciplinary cutaneous lymphoma clinic that is jointly attended and represented by the members of the multidisciplinary group in 1 physical space is the most ideal structure and interactive medium to optimize teamwork and synergy. There is 1 physical space where every patient is seen together. Thus, patients are evaluated and examined jointly, and the discussion and communication occur in real-time directly with the patient by all members. Even the pathologist joins the multidisciplinary group in clinic and reviews the biopsy slides with the team. This promotes optimal clinical-pathologic correlation in diagnosis.

Joint clinic structure offers shared resources and cost for disease-focused (“cutaneous lymphoma”) patient care.
plinary members as a group use clinic and work rooms assigned to cutaneous lymphoma manned by staff trained specifically in cutaneous lymphoma, including the nurse/new patient coordinators, medical assistant(s), and administrative staff, including front desk, phone triage, and insurance authorization. One central location for patient supplies and materials is established, accessible to each group member.

**Parallel/Individual Specialty Clinics in Adjoining Physical Space**

A parallel clinic structure is an attractive alternative to true joint clinics. This involves having individual clinics by different discipline members but in adjoining space, where if the opinion of the team member is needed, it is convenient to see the patient together because of the proximity of space and time. Typically, this type of approach occurs in institutions with comprehensive cancer centers where multiple disciplines have concurrent clinics running in proximate space. For example, the patient with advanced cutaneous T-cell lymphoma may be scheduled with the medical oncologist team member, but the dermatologist member who has an adjoining clinic can easily join the oncologist in his or her clinic, where they can jointly discuss the patient, as needed. It is unlikely that the pathologist will join the clinicians during the patient visits, given the difficulty of coordinating slide reviews across multiple concurrent clinics. However, it is essential to establish methods of easy access and efficient communication with the collaborating pathologist(s) during patient visits.

In this setting, some of the resources may be shared such as the front desk or authorization personnel, whereas they may maintain their own nursing staff with a different focus of training. The medical oncology nursing staff may not need to receive the same depth of skin-specific training that the cutaneous oncology staff may need. In most cases, the cost for each discipline will be tracked and assigned separately in this parallel clinic structure.

**Individual Specialty Clinics in Separate Physical Space**

Unfortunately, not all institutions or practices can arrange to have a joint or parallel clinic. Thus, many multidisciplinary teams may need to have clinics in completely separate spaces, where the patients may need to be seen at separate clinic locations and be evaluated by the different discipline members individually. In this model, it is paramount that the communication among the team members is carried out effectively and followed through properly.

As the clinic spaces are completely separate, the resources and cost are also distinct and separate. Both nursing and administrative personnel and their training are also separate. The training will be discipline specific. The material and supplies will be kept with each department and will be targeted to support the discipline-specific activities. If skin supplies are needed, there may need to be duplication of resources in each discipline as it would be difficult to share given the separate locations.

**Benefits and Challenges of Operational Models**

The 3 operation models of multidisciplinary care have distinct benefits and challenges. Thus, each practice or institution may select the most appropriate multidisciplinary model that serves its need and meets the available resources and goals.

**Differences in Benefits**

In joint clinics where the patient is seen by all relevant disciplines is true “one-stop shopping.” All the specialists involved in the clinical care are present in the same room to directly discuss the impression and plan with the patient. The physicians complete all of their evaluations and management discussions in the joint clinic session, so there is direct, real-time comprehensive communication with the patient and the physicians, thus minimizing any need for follow-up actions. The pathologist also has the opportunity to evaluate the patient’s clinical disease and discuss the differential diagnosis with the clinicians, which often is a means to the most appropriate clinical-pathologic diagnosis. The patient considers the risks and benefits of each treatment option during his or her visit and then can pose questions to any of the specialists without making multiple separate visits. The treatment orders (and any authorization process) can be initiated on the spot regardless of treatment type (e.g., infusional therapy, radiation treatment). Thus, this joint setting provides the greatest level of efficiency when more than 1 discipline is involved in the evaluation and management. In this joint model, the personnel, resources, and cost are disease centered: cutaneous lymphoma or cutaneous oncology. Thus, the training of personnel can be very focused, with elements more relevant to cutaneous lymphoma, and the cost can be more easily and accurately assigned and tracked. For example, a cutaneous lymphoma nursing staff can maximize their training in cutaneous lymphoma and skin management and minimize consolidation of knowledge that has less relevance to cutaneous oncology.

The primary benefit of the individual/separate clinic model is the privacy that the patient can enjoy as there are fewer care providers in the room examining the patient or involved in the discussions. Given that a comprehensive examination involves evaluating the entire skin, the experience of multiple care providers examining together can be difficult or undesirable for some patients. Other benefits include potential easier accessibility to individual disciplines if the patient need is more specific and does not require the immediate presence of multiple disciplines.
entire multidisciplinary team. For example, if it was made clear from a previous discussion that radiation therapy is the best option for a given lesion, then there is no need to be seen by the entire multidisciplinary group; rather, it may be more efficient to see the radiation oncologist alone in his or her clinic with the radiation therapy-specific personnel. The personnel training and supervision managed by each discipline in this separate clinic model may allow closer oversight, resulting in improved accountability of personnel and other resources.

The benefits of the parallel/adjoining clinic model cross over those of the joint and the individual/separate clinic models. In the parallel model, the personnel, resources, and cost structures are separately accountable in most cases, but as clinically needed, the joint clinic benefits can be made available. Opportunities for privacy are more guaranteed because those patients who do not desire evaluation by the complete complement of the multidisciplinary group can elect to arrange the visit in the clinic most relevant to their management. Thus, if carefully constructed, the parallel clinics may enjoy the benefits of the 2 alternative models.

Different Challenges
As expected, the challenges of the joint clinic model are largely the benefits of the individual clinic setting. In the joint clinic, where the patient is evaluated by multiple care providers representing each discipline, the patient privacy is compromised. Thus, adequate information should be provided for the patients before their visit to prepare their experience in a joint clinic setting. If a patient requests a more private experience, then that should be respected at the visit, and staff should limit the in-room examination and discussion to those who are essential for the care. The clinic workroom for multidisciplinary joint clinics must be able to accommodate all necessary members and their staff. This can be a problem for some practices or institutions where space is tight. With larger teams, there is more noise and a potential for more chaos and inefficiency, hence the need to keep everyone organized and delegate responsibilities whenever possible. Each institution will need to resolve the billing and cost issues of a joint clinic. In most cases, there is a single bill generated by the primary discipline coordinating the clinic rather than each discipline generating its own bills for the same patient visit. The method adopted at Stanford Cancer Center is that the primary discipline, dermatology/cutaneous oncology, provides the house staff, clinical fellows, and midlevel providers. Thus, the primary discipline captures the bill from the visit. The other disciplines receive financial benefit by either capturing downstream income (procedure, treatment, etc.) or receiving percent effort compensation in their salary assignment.

Similarly, the challenges experienced in the individual/separate clinic model are usually reflected in the benefits of the joint clinic setting. If the patient requires an evaluation and management input from more than one discipline, the patient’s visit will need to be coordinated carefully to optimize his or her experience. This is particularly the case for patients who come from far or need to adjust their work schedules. Also, because the patient’s evaluation and management discussions are not done together with the patient and discipline leaders in real time, an effort must be made to have optimal follow-up and communication after the visit with and among discipline members. The patient will receive multiple bills because each clinic will produce a bill for its discipline leader’s services. This is in contrast to the patient receiving 1 bill from the primary discipline in the joint clinic model. The individual clinic model generates more paper work and tracking time for the patient, care providers, and the institution.

As with the benefits, the parallel clinic model has challenges that cross over those of the joint clinic and the individual/separate clinic settings. When there is a need to provide a joint evaluation, the challenges that go with joint clinics come into play, whereas when the patient is seen in individual clinics, then the challenges of individual/separate clinics become relevant. The unique challenge of this parallel clinic model is the structuring and coordination of multiple disciplines to have concurrent clinics in the adjoining clinical space so one can easily activate the joint model when needed while still maintaining the benefits of the individual clinic privacy and operational efficiency. Also, if each discipline leader has full schedules, it will require a coordinated effort to ensure that the patients are seen efficiently as their needs fluctuate from joint to individual evaluation and discussion.

Multidisciplinary Environment, Additional Treats
In addition to the clinical excellence provided by a multidisciplinary teamwork, the collaborative milieu provides an environment that cultivates interactive education, mutual respect, and innovation. The dermatologist learns about how to manage toxicities of cytotoxic chemotherapies (eg, cell/growth factor support, prophylactic medications), and the oncologists learn about differential diagnoses of skin eruptions (eg, skin infections, inflammatory vs. malignant processes) and how to use skin-directed therapies (eg, topical, phototherapy). The clinicians learn about what type of biopsies and clinical information would help the pathologists, and the pathologists learn and appreciate what ancillary studies would be most helpful for the clinicians in sorting out the clinical differential diagnoses. Furthermore, a multidisciplinary environment provides a collegial check system where the members remind one another to fulfill the duties and responsibilities and help detect any errors, sooner than later. Finally, mutual curiosities foster collaborative research, whether it may be clinical, basic laboratory, or translational discoveries.

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The author has no relevant relationships to disclose.
Multidisciplinary Care in Cutaneous Lymphoma

A Look at the National Comprehensive Cancer Network Guidelines for Cutaneous Lymphomas

Pierluigi Porcu

Keywords: B-cell lymphomas, Mycosis fungoides, Sézary syndrome, Skin-directed therapy

Introduction

The National Comprehensive Cancer Network (NCCN) is a non-profit organization currently comprising 21 of the leading cancer centers in the United States. The stated goal of the NCCN, as indicated on its Web site and annual report,1,2 is to “improve the quality and effectiveness of care provided to patients with cancer.” Over the past 15 years, the NCCN has emerged as the leading source of evidence-based oncology practice guidelines, in addition to providing educational resources for patients and cancer practitioners. The NCCN also compiles and updates a Drugs and Biologics Compendium3 that offers peer-reviewed, evidence-based information designed to support decision making about the appropriate use of drugs and biologics in patients with cancer. The NCCN cancer practice guidelines are now being used not just in the United States but also abroad.2

Recognizing the growing need among clinical oncologists for diagnostic and treatment guidelines for patients with cutaneous lymphomas in the United States, the Non-Hodgkin lymphoma committee of the NCCN initiated the process of reviewing published evidence on the diagnosis and treatment of a variety of cutaneous lymphomas, with an initial emphasis on mycosis fungoides (MF) and Sézary syndrome (SS).4 Guidelines for cutaneous B-cell lymphomas (CBCLs) were developed the following year. For this purpose, ad hoc leading dermatology investigators were recruited to the committee, and subsequently retained as permanent members, to participate in the development and annual updating of the guidelines. Based on the algorithm model adopted in all previous NCCN guidelines, the MF/SS and CBCL sets included a core of diagnostic and work-up assays and imaging studies, followed by a stage-by-stage approach to treatment and surveillance, which is briefly discussed below.

Mycosis Fungoides and Sézary Syndrome

In the section addressing diagnosis and staging, one of the most challenging tasks was the selection of the best criteria to define blood involvement by MF/SS. It is well known that criteria for detection of MF/SS cells in the peripheral blood (PB) have been inconsistent and poorly reproducible.5-8 Because one of the main goals of the NCCN guidelines is to have broad and easy application across institutions and physician practices, the committee suggested a diverse approach composed of a variety of assays, including Sézary cell buffy coat preparations, multicolor flow cytometry, and T-cell receptor gene rearrangement analysis. Although any of these methodologies may be adequate for clinical use, as long as it is applied consistently, and while no combination of criteria has been universally adopted to document and monitor PB involvement with MF/SS, the NCCN guidelines suggest that the most recent International Society for Cutaneous Lymphomas (ISCL)/European Organization for Research and Treatment of Cancer (EORTC) criteria (B0-B2) are currently the most reliable.9 Further revisions of these criteria will be reflected in future NCCN guidelines.

In the work-up for MF/SS, the use of imaging studies, including computed tomography (CT) scans and positron emission tomography (PET)/CT scans, is listed as “essential” rather than “useful in selected cases,” although the specific indications for each type of imaging are left to the discretion of the treating physician. While there is consensus that imaging for sites of visceral disease is important in treatment planning for MF/SS, there is also growing concern about the overuse of CT scans in MF/SS, and these recommendations may be revised in the future. Likewise, despite its promising potential,10,11 the application of PET imaging in MF/SS has not yet been validated in controlled studies of adequate size. Patterns of use of PET imaging differ greatly among various institutions.

In the treatment section, one of the main features of the NCCN guidelines is that the algorithms for MF/SS are unique and distinct from those for most other lymphomas. Rather than following a typical “sequential” model, characterized by a progressive escalation to more intense therapy following each treatment failure, guidelines for MF/SS follow a “loop back” approach. This model recognizes 2 basic facts: (1) relapse or progression of disease is the rule, and (2) advancement to a higher stage at relapse is the exception. According to this model, supported by a large body of retrospective clinical observations12-17 and by some prospective studies,18 patients with early-stage (IA/IIA) MF/SS will likely experience recurrence with the same stage IA/IIA after each course of therapy. Progression to
more advanced skin stages (≥ T3) is observed only in a minority of patients and generally after multiple failures and long disease duration. Finally, extracutaneous extension to visceral sites is almost never observed in the absence of clear-cut progression of disease in the skin. The main goal of the “loop back” approach, therefore, is to avoid an unnecessary escalation of therapy to more intense and toxic regimens, particularly cytotoxic chemotherapy.

The recommendations for treatment of early-stage (IA/IIA) MF are consistent with currently adopted practices, focusing on skin-directed therapy and complete control of all areas of lesional skin, as determined by physical examination. Patients with more extensive skin involvement require generalized skin therapy, usually in the form of ultraviolet light, with or without 8-methoxypsoralen. Pathologic confirmation of response is not considered necessary at this point, although this recommendation may be revised once the new United States Cutaneous Lymphoma Consortium staging and response criteria become available.

For patients with advanced stage MF (≥ IIB), the guidelines offer the option of adapting therapy to the extent of skin involvement with tumors (T3). Patients with limited tumors can be approached with radiation therapy only, for local control, combined with skin-directed therapy for patch/plaque lesions. Patients with extensive tumor lesions, on the other hand, will require systemic therapy and more aggressive skin-directed therapy, such as total skin electron beam radiation therapy (TSEBRT). A list of acceptable systemic combinations is provided. The purpose of this distinction, once again, is to make sure that the appearance of a small number of tumor lesions, in the absence of other clinical indications, does not induce physicians to unnecessarily start systemic combinations or cytotoxic chemotherapy.

One of the most challenging steps in the production of the MF/SS guidelines was the development of recommendations as to (1) when to refer a patient for an allogeneic hematopoietic stem cell transplantation (alloHSCT) consultation, and (2) how to identify the ideal time to perform one. On the basis of encouraging but small, single-institution experiences,19-24 the guidelines had to offer sensible if arbitrary suggestions, mostly aimed at alerting oncologists to the fact that alloHSCT, particularly with reduced-intensity conditioning, does in fact represent a potentially curable option in highly selected patients, based on clear evidence of graft-versus-T-cell lymphoma effect. At the same time, toxicity remains significant, and the window of opportunity for this treatment modality is relatively narrow. While patients should not be offered this therapy too early, it is also important that oncologists discuss this option in patients with stage ≥ IIB MF/SS who have failed multiple systemic therapies plus an adequate trial of skin-directed therapy, so that eligibility screening and logistical arrangements can be arranged with due advance. Good performance status, lack of ongoing infections, and adequate control of disease are key criteria to optimize the success of HSCT. Preliminary data suggest that TSEBRT may represent a good modality to achieve skin control in preparation for allo-HSCT.19

For patients with SS, the guidelines suggest the immediate initiation of one or more forms of systemic therapy, including interferons, bexarotene, and extracorporeal photopheresis, in combination with generalized skin-directed therapy. New agents with promising activity in SS, such as alemtuzumab and histone deacetylase inhibitors, are currently listed among third-line treatment options, although with additional experience and data, they may be moved up to second-line.

Finally, the guidelines formally recognize the fact that subsets of patients with MF/SS, such as patients with folliculotropic MF (FMF) and those with B1 disease, display a distinct and more aggressive natural history and should be approached with a combined-modality treatment plan that includes systemic therapy, regardless of the initial stage.25-26 This recommendation is based on the observation that response to skin-directed therapy alone is suboptimal in most patients with FMF.

**Cutaneous B-Cell Lymphomas**

The NCCN is the first organization to provide American oncologists with clinical practice guidelines for primary CBCLs. Patients with CBCL often find themselves in what might be considered a “no man’s land.” While the initial clinical assessment and diagnostic biopsy is usually made in the dermatologist’s office, the discovery of a B-cell lymphoid malignancy usually prompts immediate referral to an oncologist because of the odds that the patient may have systemic disease. However, when imaging and laboratory studies (in addition to a carefully taken history addressing preexistent skin lesions) reveal that the disease is limited to the skin, oncologists are typically confronted with the fact that they have very little information about natural history and outcome for this unique category of lymphomas. This uncertainty has often resulted in the selection of unnecessarily aggressive therapy, particularly for CBCL with a significant large-cell component.

We now know that CBCL can be distinguished into 3 major subtypes: (1) primary cutaneous marginal zone lymphoma (PCMZL), (2) primary cutaneous follicle center B-cell lymphoma (PCFCCL), and (3) primary cutaneous diffuse large B-cell lymphoma, leg type (DLBCL-LT).27 The essential pathologic work-up to ensure adequate classification of these malignancies is described in the guidelines. Unlike MF/SS, where the broad need for bone marrow biopsy and imaging studies has been questioned, full-body imaging studies for CBCL are usually justified, with the possible exception of patients with solitary/regional PCMZL. Bone marrow biopsy should always be done in primary cutaneous DLBCL-LT because of the frequency of systemic spread. For PCMZL and PCFCCL, bone marrow biopsies should be done in selected cases, depending on clinical circumstance.

Primary cutaneous marginal zone lymphoma is a very indolent disease, often diagnosed in young patients. It can almost always be treated with lesional resection or low-dose involved-field radiation. It almost never disseminates beyond the skin and is associated with a near-normal life expectancy.28 Conversely, primary cutaneous DLBCL-LT is a very aggressive B-cell malignancy of the elderly that develops primarily in the skin but responds very poorly to therapy and invariably disseminates to lymph nodes and visceral sites. Survival is extremely poor.28

Between these 2 extremes, whose outcome appears to be set regardless of what one may or may not do, PCFCCL is the entity that has caused oncologists and patients the greatest amount of trouble. While PCFCCL with a homogeneous small B-cell component appears to have some immunophenotypical and biologic parallels with nodal follicular lymphomas and is approached as an indolent disease (just like PCMZL), PCFCCL with a significant large B-cell component has often in the past been classified as DLBCL. The inevitable outcome of this categorization is that patients have been
treated with combination chemotherapy and radiation, just like DLBCL, arising in other extranodal sites. In the face of a great deal of initial skepticism, a growing body of clinical observations now suggests that PCFCLs with a large-cell component do not behave like DLBCL and can be safely treated without systemic chemotherapy, as long as they do not arise in the leg.28

The evidence supporting this radically different approach to large B-cell lymphoma29–34 was carefully reviewed and integrated in the current NCCN guidelines for CBCL, which suggest a conservative and sequential approach for both PCMZL and PCFCL (regardless of the large B-cell component) is typically done for other low-grade B-cell malignancies, while supporting the use of aggressive combined-modality (chemoradiation) therapy for primary cutaneous DLBCL-LT, if the patient is able to tolerate it.

One of the greatest innovations in the guidelines for CBCL is the adoption of a new staging classification for cutaneous lymphomas other than MF/SS developed jointly by the ISCL and EORTC and published in 2007.35 This new staging system introduces much needed consistency and reproducibility in the definition of disease burden for this family of lymphomas, therefore facilitating stage-based outcome analysis across different institutions.

Conclusion

The NCCN guidelines for cutaneous lymphomas offer a flexible and up-to-date resource to educate and assist medical oncologists, dermatologists, and other cancer practitioners in the management of this relatively rare and unique family of extranodal lymphomas. Particularly in the area of CBCL, the guidelines have introduced into daily practice completely new concepts about natural history and prognosis that have challenged old treatment paradigms. Future guidelines will incorporate new disease response criteria, staging classifications, and risk stratification tools currently in development.

Disclosures

Dr. Porcu has received research funding from Millennium Pharmaceuticals, Inc. and has served as a member of a Speaker’s Bureau for AlloS Therapeutics, Inc. and THERAKOS, Inc.

References

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ADVERSE REACTIONS

The most common adverse reactions observed in patients with peripheral T-cell lymphoma (PTCL) treated with FOLOTYN were mucositis, thrombocytopenia, nausea, fatigue, and rash.

Table 4 summarizes the most frequent adverse reactions, regardless of causality, using the National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0).

**Table 4: Adverse Reactions Occurring in PTCL Patients (Incidence >10% of patients)**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Total Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>N=111</td>
<td>N=100</td>
<td>N=93</td>
<td>N=34</td>
</tr>
<tr>
<td>Mucositis</td>
<td>76</td>
<td>70</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>Trabectedin (drug)</td>
<td>44</td>
<td>44</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40</td>
<td>36</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Night sweats</td>
<td>33</td>
<td>33</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>29</td>
<td>28</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>28</td>
<td>28</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>26</td>
<td>26</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27</td>
<td>26</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>23</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>G-CSF or GM-CSF</td>
<td>22</td>
<td>22</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>21</td>
<td>19</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Ataxia</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>12</td>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12</td>
<td>12</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Summary of the most common adverse reactions**: Mucositis, thrombocytopenia, nausea, fatigue, and rash.

**Management of severe or intolerable adverse reactions**: If an adverse reaction is severe or causes substantial impairment, FOLOTYN should be withheld or discontinued. Monitoring and Dose Modifications should be considered.

**Pregnancy/nursing**: FOLOTYN can cause fetal harm when administered to a pregnant woman. FOLOTYN should be administered under the supervision of a qualified physician with experience in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

**Peripheral T-cell lymphoma**: The recommended dose of FOLOTYN is 30 mg/m² administered as an intravenous (IV) push over 3-5 minutes via the site of a free-flowing 0.9% Sodium Chloride Injection, USP IV line once weekly for 6-7 weeks in cycles, until progressive disease or unacceptable toxicity.

**Table 1: FOLOTYN Dose Modifications for Mucositis**

<table>
<thead>
<tr>
<th>Mucositis Grade</th>
<th>on Day of Treatment</th>
<th>Action</th>
<th>Dose upon Recovery to:</th>
<th>Grade 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
<td>Limit dose</td>
<td>Continue prior dose</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td>Omit dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td>Omit dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td>Stop therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: FOLOTYN Dose Modifications for Hematologic Toxicities**

<table>
<thead>
<tr>
<th>Blood Count</th>
<th>on Day of Treatment</th>
<th>Duration of Toxicity</th>
<th>Action</th>
<th>Dose upon Restart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet</td>
<td>80,000/μL or less</td>
<td>1 week</td>
<td>Limit dose</td>
<td>Continue prior dose</td>
</tr>
<tr>
<td>ANC 3,000-1,000/μL</td>
<td>or less</td>
<td>1 week</td>
<td>Omit dose</td>
<td>Continue prior dose</td>
</tr>
<tr>
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<td>with fever</td>
<td>1 week</td>
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<tr>
<td>ANC &lt;1,000/μL</td>
<td>without fever</td>
<td>1 week</td>
<td>Omit dose</td>
<td>Continue prior dose</td>
</tr>
<tr>
<td>Renal Toxicity Grade</td>
<td>on Day of Treatment</td>
<td>Action</td>
<td>Dose upon Recovery to:</td>
<td>Grade 2</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------</td>
<td>-------</td>
<td>------------------------</td>
<td>--------</td>
</tr>
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<td></td>
<td>Limit dose</td>
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<tr>
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</tr>
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</table>

**Table 3: FOLOTYN Dose Modifications for All Other Non-hematologic, Non-thrombolytic Toxicities**

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>on Day of Treatment</th>
<th>Action</th>
<th>Dose upon Recovery to:</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td></td>
<td>Limit dose</td>
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</tr>
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<td>Grade 4</td>
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**Drug Interactions**: Twenty-three percent of patients (n=25) discontinued treatment with FOLOTYN due to adverse reactions. The adverse reactions reported most frequently as the reason for discontinuation of treatment were mucositis (6% ≤ n=7) and thrombocytopenia (5%, n=3).

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<td></td>
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</tr>
<tr>
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<td>without fever</td>
<td>1 week</td>
<td>Omit dose</td>
<td>Continue prior dose</td>
</tr>
<tr>
<td>Renal Toxicity Grade</td>
<td>on Day of Treatment</td>
<td>Action</td>
<td>Dose upon Recovery to:</td>
<td>Grade 2</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------</td>
<td>-------</td>
<td>------------------------</td>
<td>--------</td>
</tr>
<tr>
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</tr>
<tr>
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<td></td>
<td>Omit dose</td>
<td></td>
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</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td>Stop therapy</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>on Day of Treatment</th>
<th>Action</th>
<th>Dose upon Recovery to:</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td></td>
<td>Limit dose</td>
<td>Continue prior dose</td>
<td></td>
</tr>
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FOLOTYN®
(pralatrexate injection)

FOLOTYN is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma.

The indication for FOLOTYN is based on overall response rate. Clinical benefit such as improvement in progression free survival or overall survival has not been demonstrated.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

FOLOTYN may suppress bone marrow function, manifested by thrombocytopenia, neutropenia, and anemia. Monitor blood counts and omit or modify dose for hematologic toxicities.

Mucositis may occur. If ≥Grade 2 mucositis is observed, omit or modify dose.

Patients should be instructed to take folic acid and receive vitamin B₁₂ to potentially reduce treatment-related hematological toxicity and mucositis.

FOLOTYN can cause fetal harm. Women should avoid becoming pregnant while being treated with FOLOTYN and pregnant women should be informed of the potential harm to the fetus.

Use caution and monitor patients when administering FOLOTYN to patients with moderate to severe renal function impairment.

Elevated liver function test abnormalities may occur and require monitoring. If liver function test abnormalities are ≥Grade 3, omit or modify dose.

Dermatologic reactions may occur. Patients with dermatologic reactions should be monitored closely, and if skin reactions are severe, FOLOTYN should be withheld or discontinued.

Adverse Reactions

The most common adverse reactions were mucositis (70%), thrombocytopenia (41%), nausea (40%), and fatigue (36%). The most common serious adverse events are pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia.

Use in Specific Patient Population

Nursing mothers should be advised to discontinue nursing or the drug, taking into consideration the importance of the drug to the mother.

Drug Interactions

Co-administration of drugs subject to renal clearance (e.g., probenecid, NSAIDs, and trimethoprim/sulfamethoxazole) may result in delayed renal clearance.

Please see brief summary of Prescribing Information on adjacent page.