

Cutaneous T-Cell Lymphoma Chemotherapy

David J. Straus, M.D.
Memorial Sloan-Kettering Cancer
Center
New York, NY

CTCL Single Agent Chemotherapy Summary

- Drugs with 40-60% response rates (~15% complete responses)- often short duration:
 - Folic acid antagonists: methotrexate, trimetrexate
 - Alkylating agents: chlorambucil, cyclophosphamide, nitrogen mustard
 - Vinca alkaloids: vincristine, vinblastine
 - Antibiotics: doxorubicin, bleomycin
 - Topoisomerase II inhibitors: etoposide, teniposide
 - Purine analogues: cladribine, pentostatin,
 - Pyrimidine analogues: gemcitabine

CTCL: low-dose methotrexate

- Average dose 25 mg orally weekly
- Mostly extensive patch/plaque (T2)
- Response rate 33% (22% PR, 12% CR)
- Median time to progression 15 mo.
- Side effects:
 - mild
 - <20% of patients
 - most frequent: mouth sores, ↓ blood cts., gi upset

Zackheim HS et al. J Am Acad Dermatol 49: 873-8, 2003

CTCL: Pentostatin

- 3.75-5.0 mg/m² by vein daily for 3 days every 3 weeks
- Relapsed with tumors, Sézary syndrome, node/organ involvement (stages IIB-IV)
- Response rate 71% (46% PR, 25% CR)
- Most responses short: 2-4 mo.
- Most frequent side effects: low white blood cell counts (30%), nausea (22%), fever (26%)

CTCL: Gemcitabine

- 1200 mg/m² by vein days 1, 8, 15 every 28 days
- MF (tumor or Sézary syndrome) and other CTCL
- Response 70% (59% PR, 11.5% CR)
- Median durations remission: PR 10 mo., CR 15 mo.
- Side effects mild: low white blood cell ct. (34%), low platelet count (25%) most frequent

CTCL

Suberoylanilide Hydroxamic Acid (SAHA) or Vorinostat

- Small molecule
- Inhibits histone deacetylation
- In vitro arrests transformed cell growth, induces differentiation and apoptosis
- Inhibits tumor growth in animals
- Phase II trial: 30% (1/22 CR) (Olsen et al. ASCO 2006, abs. 7500)

CTCL

Systemic Chemotherapy Combinations

- Comb. chemo. ± TSEBRT/top. HN2: 336 pts. (lit.) OR 81%, CR 38% (5-41 mo.) (Bunn et al., 1994)
- Rand. trial (NCI): CTX/DOX/VCR/VP16 + TSEBRT (OR 90%, CR 38%) vs. sequential Rx (top. HN2+) (OR 65%, 18%): Surv. similar, tox. ↑ for comb. (Kaye et al., 1989)

Treatment: Advanced stage CTCL

Stem Cell Transplantation

– AuPBSCT: Does not work

- 9 tumor stage pts. (IIB 5, IVA 4): 4 died, 1 NED @ 6 mo.¹

– AlloSCT: Some promise

- 8 MF/SS pts. CR including molecular (T- γ receptor gene rearr.)/cytogenetic criteria in all 8. 6 alive NED at median follow-up 56 mo.²

¹Russell-Jones et al, *Ann NY Acad Sci* 2001; 941: 147

²Molina A et al, *J Clin Oncol* 2005; 23: 6163

IRB#05-098

Phase II Trial of Doxorubicin HCl
Liposomal Injection (Doxil®) in Advanced
Stage Cutaneous T-Cell Lymphoma
Followed by Bexarotene (Targretin®)

PI: David J. Straus, M.D.

Co-PIs: Steven M. Horwitz, M.D.

Patricia L. Myskowski, M.D.

Also F. Foss (Yale), K. Hymes (NYU), M. Duvic (M.D. Anderson), A.
Goy (Hackensack)

IRB#05-098

Objectives

- Progression-free survival in patients with CTCL treated with Doxil followed by Targretin
- Major response (CR + PR) in patients with CTCL treated with Doxil followed by Targretin

IRB#05-098

Treatment Plan

- Doxil 20 mg/m² i.v. q 2 weeks x 8 doses
- Response assessment
- Targretin 300 mg/m² p.o. daily for 16 weeks
- Response assessment: CR/PR
- Continue Targretin 300 mg/m² p.o. daily until relapse

Composite Assessment (CA) of Index Lesion Disease Severity (up to 5 lesions)

- Grading score 0-8 for:
 - Scaling
 - Erythema
 - Plaque/tumor elevation
 - Hypo-/hyper-pigmentation
 - Index lesion area
- Ratio of sum of all scores divided by scores at baseline

Severity-Weighted Assessment Tool (SWAT) for CTCL

- TBSA: body divided into 12 regions with %TBSA (burn literature)
 - Pt.'s palm with 4 fingers (no thumb):1%TBSA
 - Pt.'s palm without fingers: 0.5%TBSA
 - Transparency sheet tracing of pt.'s palm+4 fingers used to measure %TBSA
- Severity Weighting Factor
 - 1=patch
 - 2=plaque
 - 4=tumor or ulceration

SWAT Skin Score

Region	% TBSA for the region	% TBSA Patch (or flat erythema)	% TBSA Plaque (or elevated/indurated erythema)	% TBSA Tumor/ Ulceration (or erythema w/fissuring, ulceration)
Head	7			
Neck	2			
Anterior Trunk	13			
Posterior Trunk	13			
Buttocks	5			
Genitalia	1			
Upper Arms	8			
Forearms	6			
Hands	5			
Thighs	19			
Lower Leg	14			
Feet	7			
% BSA by category	100			
Severity Weighting Factor		X 1	X 2	X 4
Skin Score Subtotal				

SWAT Response Criteria

Table 5.1.1a: Assessment of Overall Skin Disease^a

Assessment	Description	Status
Completely clear	No evidence of disease; 100% improvement	CCR
Marked improvement	Greater than or equal to 50% decrease in skin scores compared to baseline and improvement is maintained for 4 weeks	PR
Slight improvement	Less than 50% decrease in skin scores compared to baseline	SD
Worse	$\geq 25\%$ increase in skin scores compared to baseline while the patient is actively taking the study drug or $\geq 50\%$ increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes (should be documented by biopsy) compared to baseline while the patient is actively taking the study drug	PD

a) PR, CCR and PD must be confirmed after the initial determination

CTCL: Chemotherapy

Conclusions

- Many chemotherapy drugs are active against CTCL
- Remissions short
- Combination chemotherapy not better than single agents; combinations of CT with other agents under investigation (eg. retinoids)
- Autologous stem cell transplantation not effective
- Allogenic stem cell transplantation: interesting but toxic
- Current clinical trials employ more objective, reproducible criteria for response