January 2008 www.clinicaladvances.com Volume 6, Issue 1, Supplement 1

New Strategies in the Treatment of T-Cell Lymphoma

A Review of Selected Presentations
From the 43rd American Society
of Clinical Oncology Annual Meeting
June 1–5, 2007
Chicago, Illinois

With Commentary by
H. Miles Prince, MD, FRACP, FRCPA
Chair of Cancer Services
Peter MacCallum Cancer Centre
Professor of Medicine
University of Melbourne Medical School
Melbourne, Australia

A CME Activity
Approved for 1.0
AMA PRA
Category 1 Credit(s)™

Supported through an educational grant
from Eisai, Inc.

CME Consultants
A nationally accredited continuing medical education company

Clinical Advances in HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

Table of Contents

Included in Index Medicus/PubMed/Medline

Disclaimer

Funding for this Conference Presentations Review has been provided through an educational grant from Eisai, Inc. Support of this monograph does not imply the supporter's agreement with the views expressed herein. Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Millennium Medical Publishing, Inc., the supporters, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of CME Consultants and Millennium Medical Publishing, Inc. CME Consultants is accredited by the ACCME to provide continuing medical education for physicians.

Target Audience

This publication is specifically designed for practicing clinicians, medical oncologists, and hematologists who wish to review and update their knowledge of the treatment of T-cell lymphoma.

Educational Objectives

At the conclusion of this activity, participants should be able to:

1. Discuss the use of denileukin diftitox and liposomal doxorubicin in the treatment of cutaneous T-cell lymphoma.
2. Discuss the treatment of peripheral T-cell lymphoma with alemtuzumab plus chemotherapy.
3. Review the use of allogeneic stem cell transplantation in the treatment of T-cell lymphoma.

Credit Designation

CME Consultants designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Estimated Time to Completion

Estimated time frame for completion of the activity, including the time to complete the post-test and evaluation form, is 1 hour.

Disclosure

In direct response to the September 2004 ACCME Standards for Commercial Support, CME Consultants issued a conflict of interest policy dated January 2, 2005. The policy states that the disclosure of potential financial conflicts of interest within the last 12 months must be made and resolved prior to the date of the CME/CE activity where commercial support grants are to be used to fund the activity. The following conflicts have been managed and resolved through CME Consultants' Independent Review Committee. Our intent is to assist learners in assessing the potential for bias in information that is presented during the CME/CE activity.

The contents of some CME activities may contain discussions of nonapproved or off-label uses of some of the agents mentioned. Please consult the prescribing information for full disclosure of approved uses.

The faculty are also aware that it is their responsibility to inform the audience if discussion of any non–US Food and Drug Administration (FDA)-approved uses of pharmaceuticals, medical equipment, prostheses, etc. will be included in their presentations.

H. Miles Prince, MD, FRACP, FRCPA has nothing to disclose.

The planners, managers, and anyone in a position to control the content of CME activities are also required to report any conflicts of interest. The following conflicts have been managed and resolved through CME Consultants' Independent Review Committee:

Samantha Mattiucci, PharmD: Nothing to disclose.
Susan Coutu-Robidoux: Nothing to disclose.
Jessica Wapner: Nothing to disclose.

Discussion of Off-label/Investigational Uses of Commercial Products

This activity contains information about experimental and other uses of drugs or devices that are not currently approved by the FDA and/or other national regulatory agencies in the United States and other countries. Participants in the United States are encouraged to consult the FDA-approved product labeling for any drug or device mentioned in this program before use. Participants from other countries should consult with their respective regulatory authorities.

Commercial Supporter

This activity is supported by an educational grant from Eisai, Inc.

Original Release/Expiration Date

The original release date of this activity is January 15, 2008. The expiration date of this activity is January 15, 2009. This activity is valid for CME credit from January 15, 2008, to January 15, 2009.

How to Obtain CME Credit

To successfully complete this activity, CME Consultants requires that you read the objectives, read the monograph, take the post-test on page 15, fill out the evaluation form on page 16 and mail or fax the completed forms back to CME Consultants. Credits will only be awarded for completion of the post-test (score >70%) and return of the completed evaluation form. All documentation should be received no later than January 15, 2009.

Introduction

T-cell lymphomas are relatively rare malignancies, accounting for approximately 10–15% of all lymphomas diagnosed in the United States.[1,2] The two major types of T-cell lymphoma are peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL). Though both originate from T cells, PTCL and CTCL are distinct in terms of their associated symptoms, prognoses, and treatments. Historically, several classifications defined PTCL and CTCL, but major disparities existed between these systems. Recently a consensus was reached by the World Health Organization (WHO) and the European Organisation for Research and Treatment of Cancer (EORTC), which has helped to resolve the debate and confusion surrounding the distinction of these malignancies.[3,4]

Under the WHO/EORTC consensus, several types of PTCL are identified.[4] PTCL may occur either as predominantly disseminated, presenting mainly as adult T-cell leukemia/lymphoma, or predominantly nodal. The diagnosis of predominantly nodal PTCL is made further complex by the identification of several unique subgroups, including angioimmunoblastic T-cell lymphoma, anaplastic large-cell lymphoma (ALCL), and PTCL-not otherwise specified.

CTCL describes a wide variety of lymphomas characterized by the expansion of malignant T cells within the skin. CTCL comprises approximately 75–80% of all primary cutaneous lymphomas.[5] Originally, the only lymphomas considered to be CTCL were mycosis fungoides and Sézary syndrome. More recently, several other CTCL subgroups have been described, using a combination of clinical, histologic, and immunophenotypical criteria. According to the WHO/EORTC consensus, other malignancies now considered to be CTCL include primary cutaneous CD30+ lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and extranodal natural killer (NK)/T-cell nasal-type lymphoma (Table 1).[3,6]

Standard Therapy for T-Cell Lymphoma

Treatment of T-cell lymphoma relies heavily on the exact subtype diagnosed, and the initial treatment is determined by both disease stage and the impact of the disease on patient quality of life. Standard treatment for PTCL includes systemic chemotherapy, most often with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). However, with the exception of ALCL, most types of PTCL offer a poor prognosis, with 5-year overall survival rates between 15% and 30%.[7]

Topical therapies are commonly used to treat the skin manifestations of CTCL. These treatments include corticosteroids, mechlorethamine, and psoralen and ultraviolet A or ultraviolet B phototherapy. Systemic therapies, such as methotrexate, chlorambucil, retinoids, or low-dose interferon-α are often added to potentiate the response to the topical treatment. Patients with aggressive or metastatic disease additionally are administered radiotherapy and systemic chemotherapy, either as a single-agent or combined; however, multiagent cytotoxic regimens are palliative with no demonstrated survival benefit.[8] This lack of benefit has prompted the search for novel strategies to treat aggressive or refractory PTCL and CTCL.

Novel Treatments for T-Cell Lymphoma

The majority of new treatments under investigation for T-cell lymphoma are designed to specifically target malignant cells.[9] Recently vorinostat was approved by the US Food and Drug Administration (FDA) with an indication for progressive, persistent, or recurrent CTCL after the failure of two systemic therapies. The primary mechanism of action by which vorinostat induces cancer cell death is inhibition of histone deacetylases, causing cell cycle arrest and apoptosis.[10] FDA approval of vorinostat came after a pivotal phase II trial showed that the agent induced an overall response rate (ORR) of 29.7% in treatment-refractory patients.[11] Also currently approved in the United States for the treatment of CTCL are bexarotene, a synthetic retinoic acid agent,[12,13] and denileukin diftitox, a recombinant protein consisting of interleukin-2 (IL-2) protein sequences fused to diphtheria toxin.

There has been intense interest in the use of T cell–directed antibodies in the treatment of both PTCL and CTCL. Zanolimumab, a human monoclonal antibody, is directed against CD4, a glycoprotein present on the surface of T cells. Zanolimumab therapy resulted in an ORR of 56% in two phase II studies, and has been granted orphan drug status by the FDA.[14] Zanolimumab has been designated a Fast Track Product by the FDA, covering patients with CTCL who have failed currently available therapy, and further investigation is currently underway in an open-label phase III study in treatment-refractory patients.[15] Another monoclonal antibody, alemtuzumab, is also being tested in T-cell lymphoma. Alemtuzumab is

Table 1. WHO-EORTC Classification of CTCL

CTCL=cutaneous T-cell lymphoma; EORTC=European Organisation for the Research and Treatment of Cancer; NR=not reported; WHO=World Health Organization.

Adapted from Willemzer R et al.[3]

WHO EORTC Classification	Frequency	5-Year Survival Rate
Indolent Clinical Behavior		
Mycosis fungoides (MF)	44%	88%
MF variants and subtypes		
– Folliculotropic MF	4%	80%
– Pagetoid reticulosis	<1%	100%
– Granulomatous slack skin	<1%	100%
Primary cutaneous CD30+ lymphoproliferative disorders		
– Primary cutaneous anaplastic large cell lymphoma	8%	95%
– Lymphomatoid papulosis	12%	100%
Subcutaneous panniculitis-like T-cell lymphoma (provisional)	1%	82%
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)	2%	75%
Aggressive Clinical Behavior		
Sézary syndrome	3%	24%
Extranodal NK/T-cell lymphoma, nasal type	NR	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified	2%	16%
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)	<1%	18%
Cutaneous g/d T-cell lymphoma (provisional)	<1%	NR

directed against CD52, which is expressed on the surface of mature lymphocytes. A small study of alemtuzumab in patients with refractory CTCL showed an ORR of 60%, and several case studies also report successful treatment of CTCL and PTCL with alemtuzumab[16-19]; however, because of associated toxicities, alemtuzumab therapy requires careful monitoring throughout administration.

References

1. Evens AM, Gartenhaus RB. Treatment of T-cell non-Hodgkin's lymphoma. *Curr Treat Options Oncol*. 2004;5:289-303.
2. Evens AM, Gartenhaus RB. Molecular etiology of mature T-cell non-Hodgkin's lymphomas. *Front Biosci*. 2003;8:156-175.
3. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105:3768-3785.
4. Rizvi MA, Evens AM, Tallman MS, et al. T-cell non-Hodgkin lymphoma. *Blood*. 2006;107:1255-1264.
5. Willemze R. Cutaneous T-cell lymphoma: epidemiology, etiology, and classification. Leuk Lymphoma. 2003;44(suppl 3):S49-S54.
6. Smith BD, Wilson LD. Cutaneous lymphomas. *Semin Radiat Oncol*. 2007; 17:158-168.
7. Savage KJ. Peripheral T-cell lymphomas. *Blood Rev*. 2007;21:201-216.
8. Foss F. Overview of cutaneous T-cell lymphoma: prognostic factors and novel therapeutic approaches. *Leuk Lymphoma*. 2003;44(suppl 3):S55-S61.
9. Scheinfeld N. A brief primer on treatments of cutaneous T cell lymphoma, newly approved or late in development. *J Drugs Dermatol*. 2007;6:757-760.
10. Dokmanovic M, Clarke C, Marks PA. Histone deacetylase inhibitors: overview and perspectives. *Mol Cancer Res*. 2007;5:981-989.
11. Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 2007;25:3109-3115.
12. Zhang C, Duvic M. Treatment of cutaneous T-cell lymphoma with retinoids. *Dermatol Ther*. 2006;19:264-271.
13. Farol LT, Hymes KB. Bexarotene: a clinical review. *Expert Rev Anticancer Ther*. 2004;4:180-188.
14. Kim YH, Duvic M, Obitz E, et al. Clinical efficacy of zanolimumab (HuMax-CD4): two phase 2 studies in refractory cutaneous T-cell lymphoma. *Blood*. 2007;109:4655-4662.
15. Study of Human Monoclonal Antibody to Treat Mycosis Fungoides and Sezary Syndrome. Available online at: http://clinicaltrials.gov/ct2/show/NCT00127881?term=nct00127881&rank=1.
16. Gautschi O, Blumenthal N, Streit M, et al. Successful treatment of chemotherapy-refractory Sezary syndrome with alemtuzumab (Campath-1H). *Eur J Haematol*. 2004;72:61-63.
17. Zinzani PL, Alinari L, Tani M, et al. Preliminary observations of a phase II study of reduced-dose alemtuzumab treatment in patients with pretreated T-cell lymphoma. *Haematologica*. 2005;90:702-703.
18. Gibbs SD, Herbert KE, McCormack C, et al. Alemtuzumab: effective monotherapy for simultaneous B-cell chronic lymphocytic leukaemia and Sezary syndrome. *Eur J Haematol*. 2004;73:447-449.
19. Enblad G, Hagberg H, Erlanson M, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. *Blood*. 2004;103:2920-2924.

New Strategies in the Treatment of T-Cell Lymphoma

A Review of Selected Presentations
From the 43rd American Society
of Clinical Oncology Annual Meeting
June 1–5, 2007
Chicago, Illinois

8026 Efficacy and safety of denileukin diftitox in a phase III, double-blind, placebo-controlled study of CD25+ patients with cutaneous T-cell lymphoma[1]

A Negro-Vilar, Z Dziewanowska, ES Groves, V Stevens, JK Zhang, M Prince, A Martin, W Sterry

Despite the availability of a number of therapies to treat CTCL, many patients experience disease progression as they become refractory to these treatments,[2] which has led to the search for and development of novel treatment alternatives for these patients. One of these is denileukin diftitox. Denileukin diftitox is an engineered fusion of IL-2 protein with the active portion of diphtheria toxin. The inclusion of IL-2 allows denileukin diftitox specifically to target CTCL cells expressing the CD25 component of the IL-2 receptor[3-5]; it has been estimated that 50–60% of patients with CTCL have CD25-expressing CTCL cells.[6] After binding to the IL-2 receptor, the drug enters the cell within an acidified vesicle, where proteolytic enzymes release the enzymatically active diphtheria toxin portion of the drug.[7,8] The liberated diphtheria toxin then induces apoptotic cell death through a mechanism involving inhibition of protein synthesis.[9] Early success in phase I and II trials against CTCL paved the way for investigating the efficacy and safety of denileukin diftitox in a phase III trial.[10-12] This trial, which included patients with advanced, highly refractory CTCL, reported an ORR of 30%.[13] The results from this pivotal study led to the accelerated approval of denileukin diftitox for the treatment of advanced refractory CTCL. Here, Negro-Vilar and colleagues reported the results of a confirmatory phase III trial investigating denileukin diftitox in CTCL.[1]

A total of 144 patients with CD25+ CTCL were randomized to one of two denileukin diftitox arms (9 and 18 µg/kg per day) or intravenous (IV) placebo and received up to eight cycles of treatment (once daily for 5 days every 3 weeks). Study participants were required to have received no more than three prior therapies for CTCL. Randomization was stratified by disease status at baseline; 67% had stage IIa or less and 33% had stage IIb or greater.

The primary endpoint was ORR, defined as an improvement in tumor burden in both the skin and the blood. Confirmation of initial tumor response was required in two subsequent cycles. Both doses of denileukin diftitox induced statistically significant ORRs compared to placebo: ORRs for placebo, low-dose denileukin diftitox, and high-dose denileukin diftitox were 15.9%, 37.8% (P<.0297 vs placebo), and 49.1% (P<.0015 vs placebo), respectively (Figure 1). Complete responses (CRs) were observed in 9.1% and 11.1% of patients in the low- and high-dose denileukin diftitox groups, respectively. Disease stage had no significant effect on treatment response.

Clinical benefit was further assessed using secondary endpoints, which were found to correlate with the observed ORR. Median progression-free survival (PFS) was 794 days in the low-dose treatment arm and 971+ days in the high-dose arm, versus just 124 days in the placebo arm. The median time to first response was 92 days with high-dose denileukin diftitox, 120 days with

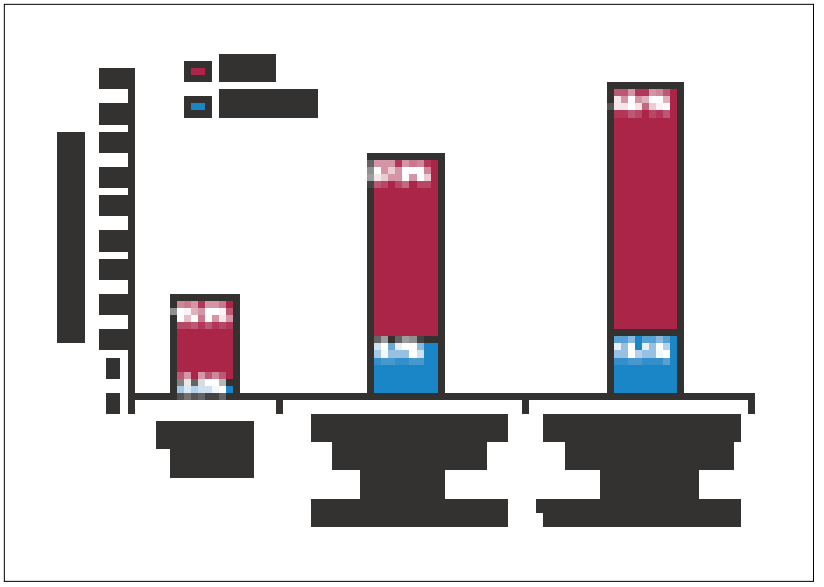

Figure 1. Overall and complete response rates among cutaneous T-cell lymphoma patients treated with denileukin diftitox versus placebo.

low-dose denileukin diftitox, and not reached at 204+ days for placebo.

Overall, denileukin diftitox was found to have a favorable safety profile at the doses used and adverse events were similar to those reported in other trials of denileukin diftitox. The only grade 3 or 4 adverse event that differed significantly between placebo and denileukin diftitox was nausea (2% versus 15% at the 18 µg/kg dose, respectively). Most adverse events noted in the denileukin diftitox treatment arms decreased markedly after the first two cycles of therapy.

This confirmatory phase III trial provided clear evidence of the safety and efficacy of denileukin diftitox for the treatment of CTCL. Importantly, this is the largest randomized and controlled trial of denileukin diftitox in CTCL to date. The clinical response and benefit observed in this study provides further support of the use of this drug as a therapeutic alternative for CTCL.

8096 Pegylated liposomal doxorubicin as an alternative treatment of cutaneous T-cell lymphoma[14]

G Quereux, A Khammari, JM Nguyen, M Benmiloud, B Dreno

CHOP therapy is an important standard treatment option for patients with aggressive or metastatic CTCL. Unfortunately, doxorubicin, one of the components of the CHOP regimen, has a low therapeutic index. At doses above 120 mg/m^2, doxorubicin induces severe neutropenia in a majority of patients.[15] Gastrointestinal discomfort, palmoplantar erythrodysesthesia, and hair loss are additional adverse effects common in patients receiving doxorubicin. Importantly, doxorubicin also induces irreversible congestive heart failure. This cardiotoxicity is cumulatively dose-related, limiting the lifetime dosage of doxorubicin that patients may receive.[16] Because these many adverse effects are often a determining factor in whether a patient is able to tolerate chemotherapy, liposomal formulations of doxorubicin have been explored as alternatives to traditional doxorubicin. Pegylated liposomal doxorubicin (PLD) is a novel formulation of doxorubicin that has been shown to induce fewer adverse effects than traditional doxorubicin.[17] In both preclinical and clinical studies, PLD exhibits pharmacokinetic properties distinctly superior to doxorubicin, including a longer distribution half-life, smaller volume of distribution, and reduced clearance.[18,19] Compared with conventional doxorubicin, PLD induces less gastrointestinal side effects, hair loss, and cardiotoxicity, while maintaining similar efficacy.[19-22] Several studies have shown that PLD is efficacious as monotherapy in CTCL, eliciting ORRs between 80% and 88%.[15,23-27] Quereux and colleagues further investigated the efficacy and safety of PLD to treat CTCL in a prospective, multicenter study.[14]

This phase II study enrolled 25 patients with advanced stage (stages II–IV) CTCL who had unsuccessfully responded to at least two previous treatments. Patients received intravenous PLD (40 mg/m^2) once

every 4 weeks. PLD therapy was given for a maximum of 8 cycles, but was reduced to as low as 4 cycles in the event of a CR. The primary study endpoint, overall response (OR), was determined at the end of treatment. An ORR of 56% (n=14) was observed in this study, with 20% of patients (n=5) achieving a CR and 36% (n=9) a partial response (PR). The statistical probability of achieving an OR was not influenced by sex or the type or stage of lymphoma. The authors noted that the ORR in this study was significantly lower than the 80–88% rate reported in other studies of PLD monotherapy for CTCL. Differences in patient populations were reasoned to be the main cause for this discrepancy, as patients in this study had advanced stage disease that was refractory to therapy. In the 14 patients who achieved an OR, the median PFS was 5.02 months (95% confidence interval [CI], 2–not achieved [NA]). Another secondary endpoint, median overall survival (OS), was calculated to be 43.7 months (95% CI, 23.4–NA). A relapse of disease was observed in 3 of the 5 patients (60%) with a CR after treatment. Disease relapse occurred at a median of 358 days. Careful analysis of the responding patients showed that PLD was effective in two subsets of CTCL that had not been previously shown: patients with Sézary syndrome and transformed CTCL responded particularly well to PLD, with ORRs of 60% and 50%, respectively.

PLD was well tolerated in this study, with the majority (80%) of adverse effects reported as grade 1 or 2. Grade 3 infections were noted in 4 individuals, including one case of pneumopathy and three cases of *Staphylococcus aureus* septicemia. However, these infections were attributed to the immunosuppression typically induced by CTCL. One patient exhibited unexplained grade 4 hyperthermia and hemophagocytosis. Importantly, the adverse effects typically noted with conventional doxorubicin therapy, gastrointestinal effects and cardiotoxicity, were only reported as mild cases in 20% and 4% of patients, respectively.

At the conclusion of this trial, the investigators found that PLD was a safe and effective monotherapy to treat CTCL. Significantly, responses were observed in this difficult-to-treat refractory patient population. Additionally, PLD was found to be particularly active in two subtypes of CTCL, Sézary syndrome and transformed CTCL. Although PLD is not a curative treatment for CTCL, the improved toxicity profile of this novel formulation compared to the traditional chemotherapy is an important approach in improving patient survival and quality of life.

8069 Alemtuzumab plus CHOP as front-line chemotherapy for patients with peripheral T-cell lymphomas[28]

J Moon, J Kim, S Sohn, D Yang, J Lee, H Kim, H Shin, J Chung, W Lee, Y Joo, S Oh

Although the CHOP regimen is considered to be the standard therapy for aggressive CTCL, it does not induce significant improvements in OS. Therefore, improving response to CHOP therapy is an important strategy for increasing survival in these patients. One approach to increase clinical response to CHOP therapy is combining it with newly available targeted biologic agents. Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen, a cell surface molecule highly expressed on malignant T cells.[29] Clinical studies of single-agent alemtuzumab have shown it to be efficacious in T-cell prolymphocytic leukemia, mycosis fungoides, Sézary syndrome, and, most recently, peripheral T-cell lymphomas (PTCL).[30-32] This latter study was a pilot trial of alemtuzumab in patients with PTCL that was either relapsed or refractory to treatment.[32] Even in this difficult to treat population, alemtuzumab elicited an ORR of 36%. Here, Moon and fellow investigators reported results from a study testing the safety and efficacy of alemtuzumab in combination with CHOP as frontline therapy for PTCL.[28] The final results of this trial were recently published.[33]

This phase II trial enrolled patients with confirmed, newly diagnosed PTCL. The median patient age was 50.5 years (range, 20–65 years) and most (70%) were male. Patients were treated with classical CHOP therapy plus alemtuzumab (10 mg on day 1 and 20 mg on day 2 of the first cycle; 30 mg on day 1 in the remaining cycles). Alemtuzumab cycles occurred in 3-week intervals. Importantly, the dosage of 30 mg every 3 weeks was chosen because of the severe infectious complications observed at higher doses in the previous PTCL study.[32] Response to treatment was measured after every 2 treatment cycles, 1 month after treatment completion, and every 3 months during the follow-up period.

A total of 20 patients were included in the analysis. An ORR of 80% (95% CI, 58.3–96.3) was observed, with 65% CR and 15% PR. Of the 4 remaining patients, 1 had stable disease and 3 experienced disease progression. At 1 year, the event-free survival was estimated to be 43.3% while the estimated rate of OS was 44.3% (Figure 2).

Because of previous experience with alemtuzumab-induced toxicities, treatment-related adverse effects were carefully monitored in this study. Grade 4 neutropenia

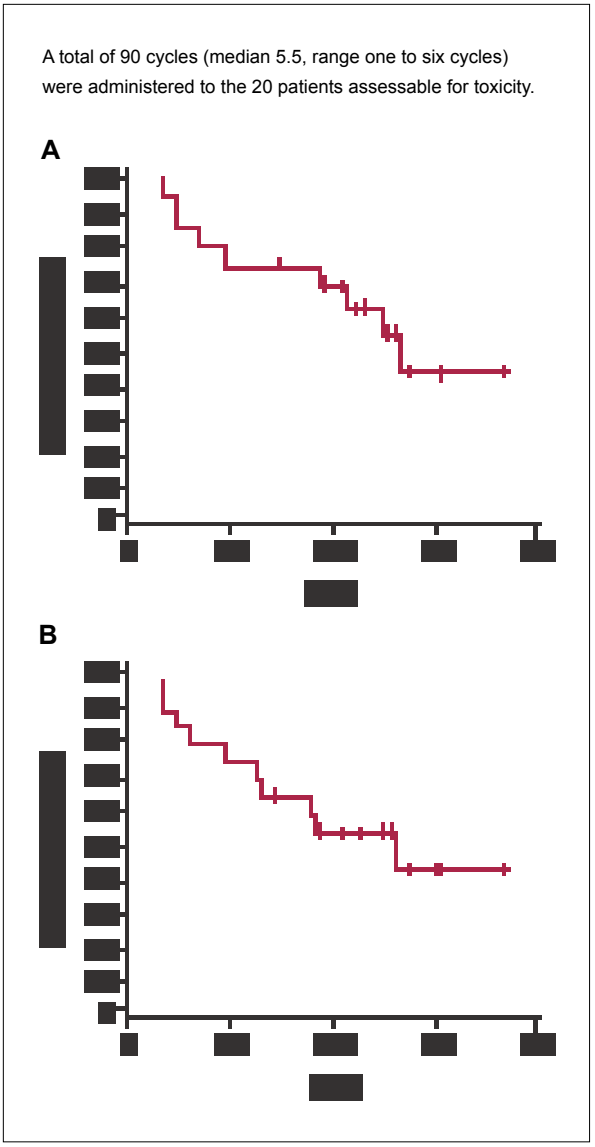

Figure 2. Survival curves: A) estimated overall survival rate and B) event-free survival rate for all patients were 44.3 and 43.3%, respectively.

and leukopenia were each noted in 90% of the patients. Commonly observed grade 3 adverse effects included anemia (25%), thrombocytopenia (30%), and febrile neutropenia (50%). After a median of 12 weeks, 5 patients (25%) experienced cytomegalovirus (CMV) reactivation, a reported complication of alemtuzumab-induced immunosuppression.[34] Although they were all treated with standard antiviral medications, 3 patients developed CMV-related diseases. Significantly, 2 patient deaths were determined to be treatment-related.

The present study by Moon and colleagues was discontinued after only 20 of the planned 43 patients were enrolled. Although the combined CHOP plus alemtuzumab chemotherapy elicited important antitumor effects in some patients, severe hematologic and infectious toxicities frequently occurred, as well as treatment-related mortalities. Therefore, future studies of alemtuzumab-based therapy for PTCL will require careful monitoring of patients and investigation of different dosage schedules to prevent treatment-related morality.

8095 Allogeneic stem cell transplantation in T-cell lymphomas: a French national survey from the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC)[35]

S Le Gouill, N Milpied, A Buzyn, G Socié, M Mothy, J Vernant, N Ifrah, C Haioun, M Michallet, C Volteau, D Blaise

Allogeneic stem cell transplantation (allo-SCT) is under increasing exploration as an alternative therapy for CTCL patients.[36] This process involves the transfer of stem cells taken from a matching donor, determined by the presence of identical human leukocyte antigens (HLA). Several studies have reported successful outcomes in individuals with CTCL following allo-SCT, with complete remissions having been noted in several cases.[37-42] Some of these cases have been associated with long-term responses. Continuous remission has been documented for up to 4.5 years after transplant. However, these studies are small, involving only one or a few patients. Therefore, further investigation of allo-SCT to treat CTCL is needed. In this report, Le Gouill and fellow investigators presented the results of a larger, multicenter study of allo-SCT in aggressive T-cell lymphoma.[35]

A retrospective analysis of T-cell lymphoma patients from the French SFGM-TC database was performed. Several factors were used to exclude patients from the analysis, including an age of less than 15 years at the time of transplantation, HIV-positive status, and evidence of lymphoblastic lymphoma. Of the 57 patients included in the analysis, 38 were male and 19 female. The median age at diagnosis was 38 years (range, 13–61 years) and a majority (n=51) of patients had an International

Prognostic Index score of 3 or more at the time of diagnosis. After diagnosis, the median time to allo-SCT was 12 months (range, 4.6–17 months). Most patients (n=42) received allo-SCT with a myeloablative conditioning regimen, in which the bone marrow activity was drastically reduced. The remaining patients (n=15) received a nonmyeloablative, or reduced intensity, conditioning regimen. Stem cells were donated from various sources, including bone marrow (n=38), circulating blood (n=18), and cord blood (n=1). All of the stem cell donors were HLA-matched; 53 donors were related to the recipient and 4 were unrelated. A variety of aggressive T-cell lymphoma subtypes were represented in this study, including PTCL (n=19), angioimmunoblastic T-cell lymphoma (n=8), anaplastic large cell lymphoma (n=20), T-cell granular lymphocytic leukemia (n=1), NK/T-cell lymphoma (n=1), localized nasal NK/ T-cell lymphoma (n=3), human T-cell leukemia/lymphotropic virus type 1 (n=2), and enteropathy-associated T-cell lymphoma (n=1).

At the time of allo-SCT, 25 patients had a CR disease status, 19 had a PR disease status, and 13 patients were categorized with either progressive or stable disease. After transplantation, 91% of the patients were found to exhibit a CR, compared to the 43% of patients who had a CR at the time of transplantation. Following transplantation, 6 patients experienced a relapse. Adverse events included 11 patients diagnosed with grade 3 or 4 graft-versus-host disease. The deaths of 18 patients were attributed to toxicity.

The results of this study, one of the largest investigating allo-SCT as therapy for aggressive T-cell lymphoma, suggest that allo-SCT may be an effective treatment strategy for CTCL patients. Because of the risk of serious adverse events and treatment-related mortality, allo-SCT may be best reserved for treating aggressive or treatment-refractory disease. The study investigators concluded that further investigation is warranted, and further evaluation of factors that may be of prognostic value is needed for clinicians to determine the best use of this therapy in the setting of advanced T-cell lymphoma.

References

1. Negro-Vilar A, Dziewanowska Z, Groves E, et al. Efficacy and safety of denileukin diftitox in a phase III, double-blind, placebo-controlled study of CD25+ patients with cutaneous T-cell lymphoma. Presentation at the 43rd American Society of Clinical Oncology Annual Meeting; Chicago, IL; June 1-5, 2007. Abstract 8026.
2. Scheinfeld N. A brief primer on treatments of cutaneous T cell lymphoma, newly approved or late in development. *J Drugs Dermatol.* 2007;6:757-760.
3. Foss F. Clinical experience with denileukin diftitox (ONTAK). *Semin Oncol.* 2006;33(1 suppl 3):S11-S16.
4. Talpur R, Jones DM, Alencar AJ, et al. CD25 expression is correlated with histological grade and response to denileukin diftitox in cutaneous T-cell lymphoma. *J Invest Dermatol.* 2006;126:575-583.
5. Jakob T, Neuber K, Altenhoff J, et al. Stage-dependent expression of CD7, CD45RO, CD45RA and CD25 on CD4-positive peripheral blood T-lymphocytes in cutaneous T-cell lymphoma. *Acta Derm Venereol.* 1996;76:34-36.
6. Foss FM, Waldmann TA. Interleukin-2 receptor-directed therapies for cutaneous lymphomas. *Hematol Oncol Clin North Am.* 2003;17:1449-1458.
7. Figgitt DP, Lamb HM, Goa KL. Denileukin diftitox. *Am J Clin Dermatol.* 2000;1:67-72; discussion 73.
8. Turturro F. Denileukin diftitox: a biotherapeutic paradigm shift in the treatment of lymphoid-derived disorders. *Expert Rev Anticancer Ther.* 2007;7:11-17.
9. Huber MA, Staib G, Pehamberger H, et al. Management of refractory early-stage cutaneous T-cell lymphoma. *Am J Clin Dermatol.* 2006;7:155-169.
10. LeMaistre CF, Saleh MN, Kuzel TM, et al. Phase I trial of a ligand fusion-protein (DAB389IL-2) in lymphomas expressing the receptor for interleukin-2. *Blood.* 1998;91:399-405.
11. Duvic M, Cather J, Maize J, et al. DAB389IL2 diphtheria fusion toxin produces clinical responses in tumor stage cutaneous T cell lymphoma. *Am J Hematol.* 1998;58:87-90.
12. Saleh MN, LeMaistre CF, Kuzel TM, et al. Antitumor activity of DAB389IL-2 fusion toxin in mycosis fungoides. *J Am Acad Dermatol.* 1998;39:63-73.
13. Olsen E, Duvic M, Frankel A, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol.* 2001;19:376-388.
14. Quereux G, Khammari A, Nguyen JM, et al. Pegylated liposomal doxorubicin (PLD) as an alternative treatment of cutaneous T-cell lymphoma. Presentation at the 43rd American Society of Clinical Oncology Annual Meeting; Chicago, IL; June 1-5, 2007. Abstract 8096.
15. Wollina U, Dummer R, Brockmeyer NH, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. *Cancer.* 2003;98:993-1001.
16. Hortobagyi GN. Anthracyclines in the treatment of cancer: an overview. *Drugs.* 1997;54 (suppl 4):1-7.
17. Waterhouse DN, Tardi PG, Mayer LD, et al. A comparison of liposomal formulations of doxorubicin with drug administered in free form: changing toxicity profiles. *Drug Saf.* 2001;24:903-920.
18. Vail DM, Amantea MA, Colbern GT, et al. Pegylated liposomal doxorubicin: proof of principle using preclinical animal models and pharmacokinetic studies. *Semin Oncol.* 2004;31(6 suppl 13):16-35.
19. Safra T, Muggia F, Jeffers S, et al. Pegylated liposomal doxorubicin (Doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m^2. *Ann Oncol.* 2000;11:1029-1033.
20. Safra T. Cardiac safety of liposomal anthracyclines. *Oncologist.* 2003;8 (suppl 2):17-24.
21. Orditura M, Quaglia F, Morgillo F, et al. Pegylated liposomal doxorubicin: pharmacologic and clinical evidence of potent antitumor activity with reduced anthracycline-induced cardiotoxicity (review). *Oncol Rep.* 2004;12:549-556.
22. Alberts DS, Muggia FM, Carmichael J, et al. Efficacy and safety of liposomal anthracyclines in phase I/II clinical trials. *Semin Oncol.* 2004;31(6 suppl 13): 53-90.
23. Pulini S, Rupoli S, Goteri G, et al. Pegylated liposomal doxorubicin in the treatment of primary cutaneous T-cell lymphomas. *Haematologica.* 2007;92: 686-689.
24. Di Lorenzo G, Di Trolio R, Delfino M, et al. Pegylated liposomal doxorubicin in stage IVB mycosis fungoides. *Br J Dermatol.* 2005;153:183-185.
25. Wollina U, Graefe T, Karte K. Treatment of relapsing or recalcitrant cutaneous T-cell lymphoma with pegylated liposomal doxorubicin. *J Am Acad Dermatol.* 2000;42(1 pt 1):40-46.
26. Wollina U, Graefe T, Kaatz M. Pegylated doxorubicin for primary cutaneous T-cell lymphoma: a report on ten patients with follow-up. *J Cancer Res Clin Oncol.* 2001;127:128-134.
27. Tsatalas C, Martinis G, Margaritis D, et al. Long-term remission of recalcitrant tumour-stage mycosis fungoides following chemotherapy with pegylated liposomal doxorubicin. *J Eur Acad Dermatol Venereol.* 2003;17:80-82.
28. Moon J, Kim J, Sohn S, et al. Alemtuzumab plus CHOP as front-line chemotherapy for patients with peripheral T-cell lymphomas. Presentation at the 43rd American Society of Clinical Oncology Annual Meeting; Chicago, IL; June 1-5, 2007. Abstract 8069.
29. Ginaldi L, De Martinis M, Matutes E, et al. Levels of expression of CD52 in normal and leukemic B and T cells: correlation with in vivo therapeutic responses to Campath-1H. *Leuk Res.* 1998;22:185-191.
30. Dearden CE, Matutes E, Cazin B, et al. High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H. *Blood.* 2001;98:1721-1726.
31. Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. *Blood.* 2003;101:4267-4272.

32. Enblad G, Hagberg H, Erlanson M, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. *Blood*. 2004;103:2920-2924.
33. Kim JG, Sohn SK, Chae YS, et al. Alemtuzumab plus CHOP as front-line chemotherapy for patients with peripheral T-cell lymphomas: a phase II study. *Cancer Chemother Pharmacol.* 2007;60:129-134.
34. Osterborg A, Karlsson C, Lundin J, et al. Strategies in the management of alemtuzumab-related side effects. *Semin Oncol.* 2006;33(2 suppl 5):S29-S35.
35. Le Gouill S, Milpied N, Buzyn A, et al. Allogeneic stem cell transplantation (allo-SCT) in T-cell lymphomas: a French national survey from the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC). Presentation at the 43rd American Society of Clinical Oncology Annual Meeting; Chicago, IL; June 1-5, 2007. Abstract 8095.
36. Knobler E. Current management strategies for cutaneous T-cell lymphoma. *Clin Dermatol.* 2004;22:197-208.
37. Masood N, Russell KJ, Olerud JE, et al. Induction of complete remission of advanced stage mycosis fungoides by allogeneic hematopoietic stem cell transplantation. *J Am Acad Dermatol.* 2002;47:140-145.
38. Guitart J, Wickless SC, Oyama Y, et al. Long-term remission after allogeneic hematopoietic stem cell transplantation for refractory cutaneous T-cell lymphoma. *Arch Dermatol*. 2002;138:1359-1365.
39. Soligo D, Ibatici A, Berti E, et al. Treatment of advanced mycosis fungoides by allogeneic stem-cell transplantation with a nonmyeloablative regimen. *Bone Marrow Transplant*. 2003;31:663-666.
40. Fijnheer R, Sanders CJ, Canninga MR, et al. Complete remission of a radiochemotherapy-resistant cutaneous T-cell lymphoma with allogeneic non-myeloablative stem cell transplantation. *Bone Marrow Transplant*. 2003;32:345-347.
41. Herbert KE, Spencer A, Grigg A, et al. Graft-versus-lymphoma effect in refractory cutaneous T-cell lymphoma after reduced-intensity HLA-matched sibling allogeneic stem cell transplantation. *Bone Marrow Transplant.* 2004;34:521-525.
42. Molina A, Zain J, Arber DA, et al. Durable clinical, cytogenetic, and molecular remissions after allogeneic hematopoietic cell transplantation for refractory Sezary syndrome and mycosis fungoides. *J Clin Oncol.* 2005;23:6163-6171.

Commentary

H. Miles Prince, MD, FRACP, FRCPA

Peter MacCallum Cancer Centre and the University of Melbourne Medical School, Melbourne, Australia

Primary cutaneous T-cell lymphomas are rare diseases with an incidence of approximately 0.5 per 100,000. The majority of patients with CTCL have mycosis fungoides, and, of these, approximately 80% have early-stage disease. The trials presented here focus on a relatively rare group of patients with CTCL—those with advanced-stage disease. Advanced-stage disease includes patients with tumor-stage, erythrodermic, nodal, or visceral involvement of disease. Such patients typically die of their disease (unlike patients with very early-stage mycosis fungoides, who have a survival similar to their age-matched counterparts), and so new treatment approaches are needed.

Typical treatment strategies for patients with advanced-stage disease include biologic response modifiers such as interferon-α, rexinoids such as bexarotene, and systemic chemotherapy. Currently approved therapies in the United States for relapsed/refractory advanced-stage CTCL are bexarotene, denileukin diftitox, and more recently the histone deacetylase inhibitor vorinostat.

The study by Negro-Vilar et al[1] is the first placebo-controlled trial in CTCL. Responses to denileukin diftitox were observed in patients with both early- and advanced-stage disease; patients had failed up to three prior therapies including systemic therapies, thus they were a very poor prognosis group of patients—demonstrated by a PFS of only 124 days in those who received placebo. The efficacy of denileukin diftitox was clearly demonstrated by a statistically significant increased ORR, which translated into a striking improvement in PFS, with a median PFS of more than 2 years. Moreover, there was a distinct trend of improved ORR and PFS in the higher-dose arm of denileukin diftitox. Although not a simple drug to deliver, requiring daily treatment for 5 consecutive days every 3 weeks, its side effect profile was acceptable, but toxicities of peripheral edema and fluid retention required careful monitoring. The observed toxicities need to be placed into context of other studies that have demonstrated that the toxicity profile of denileukin diftitox can be further improved with the concomitant use of corticosteroids.[2] Of note, this study involved only patients with CD25+ CTCL. It is already recognized that patients with CD25– disease also respond to denileukin diftitox.[3] Thus we await the results of long-term follow up of patients with CD25– disease to see if their outcome is as favorable as those with CD25+ CTCL.[4] Given these definitive results, denileukin diftitox has a clear place in the therapy of CTCL and further studies examining combination therapies are warranted.

The study by Quereux et al[5] of liposomal doxorubicin confirmed prior studies that patients with advanced-stage CTCL respond to this drug.[6] Indeed, the observed ORR of 56% was impressive given that these patients were heavily pretreated. Within this cohort of patients there were two groups of CTCL patients that deserve particular attention, namely those with Sézary syndrome, the leukemic form of mycosis fungoides, and those with transformed disease. Both groups are recognized to have a particularly poor prognosis and both groups also responded to liposomal doxorubicin, with response rates of 60% and 50%, respectively. These response rates are very promising for a single agent and further studies are warranted to study this drug in the context of combination therapy. Nonetheless, the value of liposomal doxorubicin, either alone or in combination, needs to be defined by comparing it to standard doxorubicin in a randomized controlled trial. Such studies will definitively determine if liposomal doxorubicin is superior to standard doxorubicin.

To put this study into context, two other relatively new systemic chemotherapy agents are worthy of discus-

sion—gemcitabine and forodesine. Duvic and colleagues have investigated the safety and efficacy of gemcitabine monotherapy for CTCL.[7] Twenty-five patients with CTCL on a phase II open-label trial received intravenous gemcitabine (1,000 mg/m^2) on days 1, 8, and 15 for 6 cycles or more. Responses were seen in 17 of 25 study patients (68%). Gemcitabine was generally well tolerated, with myelosuppression being the major toxicity. In a study by Marchi and coworkers, 32 previously untreated patients with mycosis fungoides (n=26), PTCL with exclusive skin involvement (n=5), or Sézary syndrome (n=1) were given gemcitabine on days 1, 8, and 15 of a 28-day schedule at a dose of 1200 mg/m^2 intravenously over 30 minutes for a total of 6 cycles.[8] Seven patients (22%) achieved a CR and 17 (53%) achieved a PR. Further studies using gemcitabine in combination, either contemporary or sequentially, with other drugs in patients with advanced-stage untreated CTCL are needed.

Forodesine is a potent, rationally designed purine nucleoside phosphorylase (PNP) inhibitor that is orally bioavailable. Duvic et al performed an open-label dose-escalation study of forodesine, 40–320 mg/m^2 daily for 4 weeks, to evaluate the safety and pharmacokinetic profile of oral forodesine, followed by an investigation of the expansion of the optimal biologic dose (dose with maximum PNP inhibition and elevation of plasma deoxyguanosine levels) to assess efficacy.[9] Previously treated, refractory CTCL patients with stage Ib or greater disease were eligible for participation. The primary endpoint was ORR, as measured by the severity-weighted assessment tool (SWAT) and physicians' global assessment (PGA). Overall, 37 patients were treated and no dose-limiting toxicities were observed with target doses of 320 mg/m^2. Based on pharmacokinetic and pharmacodynamic results, 80 mg/m^2 per day was identified as the optimal biologic dose. The ORR was 54% (15 of 28 patients; 2 [7.1%] with a CR and 13 [46.4%] with a PR). The proportion of patients with stage IIb or greater disease was 68%. Response in this population was seen in 10 (53%) of the 19 patients (1 [5%] with a CR and 9 [47%] with a PR). The percent change in SWAT score from baseline as a function of time demonstrated a progressive decrease over a 24-week period. The most common adverse events classified as grade 2 or less, without regard to causality, were nausea (30%), dizziness (22%), pruritus (22%), fatigue (19%), headache (19%), peripheral edema (19%), and pyrexia (16%). The only adverse event classified as grade 3 or greater, without regard to causality, and occurring in at least 2 patients, was lymphopenia, which was observed in 2 patients (5%).

Alemtuzumab is a humanized monoclonal antibody directed against the pan-lymphocyte antigen CD52. It has demonstrable single-agent activity in CTCL, with an ORR of approximately 40% in patients with previously treated disease.[10,11] It has also shown single-agent activity in PTCL.[12] Moon et al[13] extended this observation and combined alemtuzumab with conventional-dose combination therapy in the form of CHOP. As opposed to the other studies in this review, these patients all had PTCL rather than CTCL. There are three important aspects to this study worthy of comment. Firstly, the alemtuzumab was administered in a novel fashion of 30 mg/m^2 IV on day 1 of the 21-day cycles. Single-agent trials of alemtuzumab have typically administered alemtuzumab three times per week for 12–16 weeks. Whether an intermittent schedule as described in this study is as effective as the more dose-intense schedule is unknown. Secondly, the response rate was impressive, with 13 CRs and 3 PRs giving an ORR of 80% and estimated 1-year event-free survival of 43%. Thirdly, toxicity was substantial, with a high incidence of grade 4 neutropenia and associated febrile neutropenia. In addition, one quarter of the study patients experienced CMV reactivation, leading in 3 cases to CMV-related pneumonitis and retinitis. The high incidence of cytopenias and CMV reactivation with alemtuzumab has been noted previously,[14] and these complications limit the capacity of combination therapy. Moreover, the intensive infection prophylaxis and CMV monitoring add to the cost of this approach.[15]

Zanolimumab is a fully human anti-CD4 monoclonal antibody that is specific to the CD4 receptor, and recently two phase II studies have demonstrated efficacy in CTCL.[16] The response rate is promising and the toxicity profile appears better than with alemtuzumab (probably due to the pan-lymphocyte toxicity of alemtuzumab). Thus, further studies of zanolimumab in combination with chemotherapy are likely to follow in both CTCL and PTCL.

Probably the most aggressive therapy for CTCL and PTCL is allogeneic transplantation. Although there is clearly a graft-versus-lymphoma (GVL) effect in CTCL, as demonstrated in a number of studies,[17-26] the GVL effect is unproven in PTCL.[27] The survey of allogeneic stem cell transplants in T-cell lymphomas by Le Gouill et al[28] identified 57 cases from 10 French centers. The median age was low at 38 years, and almost half were treated in CR. Although the authors claim that this study confirms the role of a GVL effect, this claim is not convincing in this review and the GVL effect still remains unproven. Moreover, the transplant-related mortality of 18 of 57 patients is high and consistent with previous registry reports.[27] Nonetheless, the promising findings with allogeneic transplant for PTCL warrant further exploration of this modality in both PTCL and CTCL, though given the high rate of transplant-related mortality careful patient selection is required.

These studies clearly demonstrate that we are expanding our treatment options for T-cell lymphomas—both CTCL and PTCL. They also highlight that the primary difficulty of studying new therapies in these diseases is their relative rarity compared to B-cell lymphomas, which is made even more complex given the heterogeneous nature of PTCL. In most studies a variety of subtypes of PTCL are included. It would be somewhat naive to believe that all these subtypes behave in a similar fashion, which complicates how a clinician should interpret the data for an individual patient.

Nonetheless, we know we must improve the outcome for the patients with anaplastic lymphoma kinase–negative systemic PTCL—lymphomas that are known to have a poor outcome with CHOP-like regimens. Thus, upfront regimens that combine conventional-dose chemotherapy with novel agents such as alemtuzumab or liposomal doxorubicin need to be tested in randomized trials. Other agents that could be considered for combination with standard chemotherapy include bexarotene, the histone deacetylase inhibitor vorinostat, or the CD4-specific antibody zanolimumab.[16] Another approach would be to consider maintenance strategies utilizing these agents.

Denileukin diftitox has yet to be fully assessed in PTCL, with one study published to date. Dang and colleagues performed a phase II study of denileukin diftitox in relapsed/refractory T-cell non-Hodgkin lymphoma, excluding cutaneous T-cell lymphoma.[29] Eligible patients received denileukin diftitox 18 µg/kg per day for 5 days every 3 weeks for up to eight cycles. For 27 patients enrolled, objective responses (6 CRs, 7 PRs) were achieved in 13 patients (48.1%), 8 patients (29.6%) had stable disease, and 6 patients (22.2%) had progressive disease. An objective response was achieved in 8 of 13 patients (61.5%) with CD25+ tumors (4 CRs, 4 PRs) and 5 of 11 patients (45.5%) with CD25– tumors (2 CRs, 3 PRs). Median PFS was 6 months (range, 1–38+ months).

Given that advanced-stage CTCL is incurable, treatment is aimed at improving disease-free survival and quality of life. Thus, most patients have a variety of therapeutic options open to them, which makes determining a standard treatment paradigm almost impossible. In general, chemotherapy is avoided for as long as possible, and the good toxicity profiles of bexarotene and vorinostat make them appealing first-line systemic therapies for CTCL. Although the toxicity of denileukin diftitox is clearly greater than that of these two agents, durable PFS makes denileukin diftitox a very appealing agent as first- or second-line therapy in advanced-stage CTCL.

With respect to vorinostat, a single center, phase II, dose-finding trial of oral vorinostat to determine response rate and response duration in patients with relapsed or refractory stage Ia–IVb CTCL has been performed.[30] Thirty-three patients, 28 with advanced-stage CTCL, with a median of five prior therapies (range, 1–15) were enrolled in one of three sequential dosing cohorts. Response to therapy was categorized according to the PGA. Eight patients achieved a PR, including 7 patients with advanced-stage disease and 4 with Sézary syndrome. The median time to response and time to progression for responders were 11.9 and 30.2 weeks, respectively. Moreover, 14 of 31 evaluable patients had relief from pruritus. Responses were observed in all stages of the disease, including patients with early-stage refractory mycosis fungoides, tumors with large cell transformation, and those with nodal and blood involvement. The most common drug-related side effects of fatigue, thrombocytopenia, and gastrointestinal upset were generally well tolerated, and the 400 mg daily regimen appeared to have the most favorable safety profile. Another single-arm, open-label, phase IIb trial of vorinostat was conducted with 74 heavily pretreated patients whose previous treatments had included bexarotene.[31] Sixty-one patients had at least stage IIb disease. The primary endpoint of the trial was overall response by the modified SWAT scores. The ORR was 29.7% in patients with stage IIb disease and 29.5% in patients with higher stage disease. Median time to response was 56 days for patients with stage IIb or higher. Median duration of response was not reached but estimated to be greater than 185 days, while the median time to progression was 4.9 months overall and 9.8 months for stage IIb or higher responders. Approximately one third of patients had relief from their pruritus. The most common drug-related adverse events were again diarrhea, fatigue, nausea, and anorexia. Consequently, vorinostat has recently been approved by the FDA for patients who have progressive, persistent, or recurrent CTCL following two prior systemic treatments.[32]

Another promising histone deacetylase inhibitor is romidepsin (depsipeptide). The preliminary results of 71 patients with CTCL showed an ORR of 31%, with a CR observed in 4 patients, a PR in 18 patients, and stable disease in 9 patients. The median duration of response was 17 months, 5.5+ months, and 6+ months, respectively. One patient remained in an ongoing CR, off therapy, after 5 years, and one patient who has achieved a PR continues to receive romidepsin for greater than 69 months.[33] Response to romidepsin in CTCL was confirmed in a transatlantic study of patients with stage Ib–IVa CTCL/Sézary syndrome.[34] In this study of 31 evaluable patients who had received a median of three prior systemic therapies including prior chemotherapy, an ORR of 39%, with an 8% CR rate, was observed. Moreover, a further 58% had stabilization of their disease and 53% of all patients demonstrated relief of pruritus. The median time to response for these patients was 2 months. Of interest, in vivo treatment with romidepsin has been shown to upregulate expression of the IL-2 receptor, the

target for denileukin diftitox. Romidepsin was shown to increase the sensitivity of this cell line to denileukin diftitox with a synergistic increase in apoptosis.[35]

The response rates and PFS observed with the histone deacetylase inhibitors appear comparable to those observed with bexarotene. Although the impressive PFS observed with denileukin diftitox would suggest that it may achieve better outcomes, one needs to recognize that the patient populations in the various studies were somewhat different and there is yet to be a head-to-head comparison of denileukin diftitox to vorinostat.

Finally, extracorporeal photopheresis is a treatment modality that is particularly effective for erythrodermic mycosis fungoides or Sézary syndrome, and combination therapies with vorinostat, bexarotene, or some of the agents described in this review warrant further study.

References

1. Negro-Vilar A, Dziewanowska Z, Groves E, et al. Efficacy and safety of denileukin diftitox in a phase III, double-blind, placebo-controlled study of CD25+ patients with cutaneous T-cell lymphoma. Presentation at the 43rd American Society of Clinical Oncology Annual Meeting; Chicago, IL; June 1-5, 2007. Abstract 8026.
2. Foss FM, Bacha P, Osann KE, Demierre MF, Bell T, Kuzel T. Biological correlates of acute hypersensitivity events with DAB(389)IL-2 (denileukin diftitox, ONTAK) in cutaneous T-cell lymphoma: decreased frequency and severity with steroid premedication. *Clin Lymphoma*. 2001;1:298-302.
3. Talpur R, Jones DM, Alencar AJ, et al. CD25 expression is correlated with histological grade and response to denileukin diftitox in cutaneous T-cell lymphoma. *J Invest Dermatol*. 2006;126:575-583.
4. Negro-Vilar A, Dziewanowska Z, Groves E, Lombardy E, Stevens V. Phase III study of denileukin diftitox (ONTAK) to evaluate efficacy and safety in CD25+ and CD25- cutaneous t-cell lymphoma patients. *Blood (ASH Annual Meeting Abstracts)*. 2006;108. Abstract 696.
5. Quereux G, Khammari A, Nguyen JM, et al. Pegylated liposomal doxorubicin (PLD) as an alternative treatment of cutaneous T-cell lymphoma. Presentation at the 43rd American Society of Clinical Oncology Annual Meeting; Chicago, IL; June 1-5, 2007. Abstract 8096.
6. Wollina U, Dummer R, Brockmeyer NH, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. *Cancer*. 2003;98:993-1001.
7. Duvic M, Talpur R, Wen S, Kurzrock R, David CL, Apisarnthanarax N. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. *Clin Lymphoma Myeloma*. 2006;7:51-58.
8. Marchi E, Alinari L, Tani M, et al. Gemcitabine as frontline treatment for cutaneous T-cell lymphoma: phase II study of 32 patients. *Cancer.* 2005;104: 2437-2441.
9. Duvic M, Forero-Torres A, Foss F, Olsen EA, Kim Y. Oral forodesine (Bcx-1777) is clinically active in refractory cutaneous t-cell lymphoma: results of a phase I/II study. *Blood (ASH Annual Meeting Abstracts)*. 2006;08. Abstract 2467.
10. Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. *Blood*. 2003;101:4267-4272.
11. Kennedy GA, Seymour JF, Wolf M, et al. Treatment of patients with advanced mycosis fungoides and Sézary syndrome with alemtuzumab. *Eur J Hematol.* 2003;71:250-256.
12. Enblad G, Hagberg H, Erlanson M, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. *Blood.* 2004;103:2920-2924.
13. Moon J, Kim J, Sohn S, et al. Alemtuzumab plus CHOP as front-line chemotherapy for patients with peripheral T-cell lymphomas. Presentation at the 43rd American Society of Clinical Oncology Annual Meeting; Chicago, IL; June 1-5, 2007. Abstract 8069.
14. Gibbs SDJ, Westerman DA, Seymour JF, Prince HM. Severe and prolonged myeloid hematopoietic toxicity following alemtuzumab therapy in patients with peripheral T-cell lymphoproliferative disorders. *Br J Haematol.* 2005;130:87-91.
15. Thursky KA, Worth LJ, Seymour JF, Prince HM, Slavin MA. A review of spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab. *Br J Haematol.* 2005;132:3-12.
16. Kim YH, Duvic M, Obitz E, et al. Clinical efficacy of zanolimumab (HuMax-CD4): two phase 2 studies in refractory cutaneous T-cell lymphoma. *Blood.* 2007;l:4655-4662.
17. Burt RK, Guitart J, Traynor A, et al. Allogeneic hematopoietic stem cell transplantation for advanced mycosis fungoides: evidence of a graft-versus-tumor effect. *Bone Marrow Transplant.* 2000;25:111-113.
18. Fijnheer R, Sanders CJG, Canniga MR, de Weger RA, Verdonck LF. Complete remission of a radiochemotherapy-resistant cutaneous T-cell lymphoma with allogeneic non-myeloablative stem cell transplantation. *Bone Marrow Transplant.* 2003;32:345-347.
19. Gabriel IH, Olavarria E, Jones RR, Whittaker SJ, Chaidos A, Apperley JF. Graft versus lymphoma effect after early relapse following reduced intensity sibling stem cell transplantation for relapsed cytotoxic variant of mycosis fungoides. *Bone Marrow Transplant*. 2007;40: 401-403.
20. Guitart J, Wickless SC, Oyama Y, et al. Long-term remission after allogeneic hematopoietic stem cell transplantation for refractory cutaneous T-cell lymphoma. *Arch Dermatol.* 2002;138:1359-1365.
21. Herbert KE, Spencer A, Grigg A, Ryan G, McCormack C, Prince HM. Graft-versus-lymphoma effect in refractory cutaneous T-cell lymphoma after reduced-intensity HLA-matched sibling allogeneic stem cell transplantation. *Bone Marrow Transplant.* 2004;34:521-525.
22. Massod N, Russell KJ, Olerud JE, et al. Induction of complete remission of advanced stage mycosis fungoides by allogeneic hematopoietic stem cell transplantation. *J Am Acad Dermatol.* 2002;47:140-145.
23. Molina A, Nademanee A, Arber DA, Forman SJ. Remission of refractory Sézary syndrome alter bone marrow transplantation from a matched unrelated donor. *Biol Blood Marrow Transplant.* 1999;5:400-404.
24. Molina A, Zain J, Arber DA, et al. Durable clinical, cytogenetic, and molecular remissions after allogeneic hematopoietic cell transplantation for refractory Sezary syndrome and mycosis fungoides. *J Clin Oncol*. 2005;23:6163-6171.
25. Onida F, Saporiti G, Berti E, et al. Reduced-intensity conditioning allogeneic haematopoietic stem cell transplantation in advanced mycosis fungoides and Sézary syndrome. *Bone Marrow Transplant.* 2007;39(suppl1):S40. Abstract O360.
26. Soligo D, Ibatici A, Berti E, et al. Treatment of advanced mycosis fungoides by allogeneic stem-cell transplantation with a nonmyeloablative regimen. *Bone Marrow Transplant*. 2003;31:663-666.
27. Feyler S, Prince HM, Pearce R, et al. The role of high dose therapy and stem cell rescue in the management of T-cell malignant lymphomas: a BSBMT and ABMTRR study. *Bone Marrow Transplant*. 2007;40:443-450.
28. Le Gouill S, Milpied N, Buzyn A, et al. Allogeneic stem cell transplantation (allo-SCT) in T-cell lymphomas: a French national survey from the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC). Presentation at the 43rd American Society of Clinical Oncology Annual Meeting; Chicago, IL; June 1–5, 2007. Abstract 8095.
29. Dang NH, Pro B, Hagemeister FB, et al. Phase II trial of denileukin diftitox for relapsed/refractory T-cell non-Hodgkin lymphoma. *Br J Haematol.* 2007;136: 439-447.
30. Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). *Blood.* 2007;109:31-39.
31. Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol.* 2007;25:3109-3115.
32. Mann BS, Johnson JR, He K, et al. Vorinostat for treatment of cutaneous manifestations of advanced primary cutaneous T-cell lymphoma. *Clin Cancer Res.* 2007;13:2318-2322.
33. Piekarz R, Frye R, Wright J, et al. Update of the NCI multiinstitutional phase II trial of romidepsin, FK228, for patients with cutaneous or peripheral T-cell lymphoma. *J Clin Oncol (Meeting Abstracts).* 2007;25(18 suppl). Abstract 8027.
34. Lerner A, Demierre MF, Whittaker S, et al. Romidepsin (depsipeptide, FK228) induces clinically significant responses in treatment-refractory CTCL: interim report of a phase ii multicenter study. *Blood (ASH Annual Meeting Abstracts)*. 2006;108(11): Abstract 2468.
35. Piekarz RL, Robey RW, Zhan Z, et al. T-cell lymphoma as a model for the use of histone deacetylase inhibitors in cancer therapy: impact of depsipeptide on molecular markers, therapeutic targets, and mechanisms of resistance. *Blood.* 2004;103:4636-4643.

New Strategies in the Treatment of T-Cell Lymphoma

CME Post-Test: *Circle the correct answer for each question below.*

1. The novel CTCL therapy denileukin diftitox is a fusion of _____ with diphtheria toxin.

   a. IL-1
   b. IL-2
   c. IL-3
   d. CD25

2. A phase III trial reported by Negro-Vilar and colleagues showed that low and high doses of denileukin diftitox therapy induced overall response rates of _____ and _____, respectively.

   a. 37.8%; 49.1%
   b. 15.9%; 37.8%
   c. 15.9%; 49.1%
   d. 9.1%; 11.1%

3. Patients receiving low-dose (9 mg/kg/day) denileukin diftitox treatment experienced a median PFS of _____ days.

   a. 473 b. 571
   c. 794 d. 971

4. In a study by Quereux and fellow investigators, _____ of patients had a response to pegylated liposomal doxorubicin treatment.

   a. 20% b. 36%
   c. 56% d. 60%

5. In these patients who had a response to pegylated liposomal doxorubicin, the median PFS was _____ months.

   a. 3.75 b. 5.02
   c. 6.45 d. 9.52

6. Cardiotoxicity, a dosage-limiting adverse effect of traditional doxorubicin, occurred at a rate of _____ in patients receiving pegylated liposomal doxorubicin in the Quereux study.

   a. 4% b. 16%
   c. 20% d. 30%

7. Alemtuzumab is a humanized monoclonal antibody directed against _____.

   a. CD4
   b. CD12
   c. CD25
   d. CD52

8. True or false? A phase II trial of alemtuzumab in combination with CHOP was discontinued due to treatment-related toxicities.

   a. True b. False

9. As reported by Moon and colleagues, the combination of alemtuzumab and CHOP therapy resulted in an overall response rate of _____ in patients with PTCL.

   a. 15% b. 45%
   c. 65% d. 80%

10. In a retrospective study of allogeneic stem cell transplantation in aggressive T-cell lymphoma, _____ of patients had a CR following transplantation.

    a. 45% b. 57%
    c. 85% d. 91%

CERTIFICATE REQUEST FORM

First name _____ MI _____ Last name _____

Telephone _____ Fax _____ E-mail _____

Institution _____ Department _____

Address _____

City _____ State _____ Zip _____

Certificate type: ☐ Physician ☐ Other

May we contact you in the future to participate in a short post-activity evaluation? Yes No

Approximately how many minutes did it take you to complete this CME activity, including the post-test and evaluation? _____

I certify that I have completed this CME activity as designated.

Signature _____ Date _____

Job Code: JE7085127

New Strategies in the Treatment of T-Cell Lymphoma

Evaluation Form

Initial release date: January 15, 2008; material expires one year from release date: January 15, 2009.

Please complete the CME post-test, the Certificate Request Form, and this evaluation form and return to: CME Consultants, 94 Main St., Wakefield, RI 02879. Answers should be submitted no later than January 15, 2009. Please read the instructions below.

This activity is designated for 1.0 *AMA PRA Category 1 Credit(s)*™. In order to receive your CME credit(s) you are requested to review the material in full and take the post-test on page 15. Once you have completed the quiz, please note in the space provided on the Certificate Request Form the amount of time it took you to complete the entire activity, including the post-test and evaluation.

Thank you for completing the evaluation form. Your evaluation of the activity and comments are important to us and will remain confidential.

Please answer the following questions by circling the number that best reflects your view.
(Scale: 1 = poor; 2 = fair; 3 = satisfactory; 4 = good; 5 = excellent)

1. Please rate how effectively you are able to:

a. Discuss the use of denileukin diftitox and liposomal doxorubicin in the treatment of cutaneous T-cell lymphoma.	1	2	3	4	5
b. Discuss the treatment of peripheral T-cell lymphoma with alemtuzumab plus chemotherapy.	1	2	3	4	5
c. Review the use of allogeneic stem cell transplantation in the treatment of T-cell lymphoma.	1	2	3	4	5

2. Activity/Topic:

a. The extent this program met your continuing professional development goals	1	2	3	4	5
b. The overall quality of the activity	1	2	3	4	5
c. The overall format of the activity	1	2	3	4	5
d. The applicability/usefulness of the material to your practice Not in practice ☐	1	2	3	4	5

3. Based on your previous knowledge and experience, this activity was:

Too basic ☐ Appropriate ☐ Too complex ☐

4. Do you feel that the activity was objective, balanced, and free of commercial bias? Yes No

If no, why? _____

5. Based on this activity, how might you change your practice management or patient care?

_____

6. Please list any speakers and/or topics you would like in future programs.

_____

7. Would a periodic review of this or related material be appropriate? Yes No

8. We welcome your comments _____

_____

_____

CME Consultants
A nationally accredited continuing medical education company

94 Main Street, Wakefield, RI 02879
Phone: (401) 789-4413 Fax: (401) 789-4366
www.cmeconsultantsinc.com

Job Code: JE7085127