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Recent Advances in the Treatment of T-cell Lymphomas

A Review of Selected Presentations From
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This activity has been designed to meet the educational needs of hematologists and oncologists involved in the management of patients with T-cell lymphomas.

Statement of Need/Program Overview

Data are emerging on novel agents as well as new combination regimens for the treatment of lymphoma. This monograph reviews some of the salient new data recently presented at international meetings of hematologists/oncologists.

Educational Objectives

After completing this activity, the participant should be better able to:

1. Describe the importance of new study findings in the form of selected abstracts/poster summaries from American Society of Hematology (ASH) 2009 in the natural history of T-Cell Lymphoma.
2. Assess the results of these new study findings including current clinical trials evaluating therapy in the treatment of T-Cell Lymphoma.
3. Integrate into clinical practice the latest knowledge and methods for treating patients with T-Cell Lymphoma.
4. Identify future research directions for all therapies in T-Cell Lymphoma.

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Recent Advances in the Treatment of T-cell Lymphomas

1657 Final Results of a Phase 2 NCI Multicenter Study of Romidepsin in Patients with Relapsed Peripheral T-Cell Lymphoma (PTCL)[1]

R Piekarz, J Wright, R Frye, SL Allen, D Joske, M Kirschbaum, ID Lewis, M Prince, S Smith, ES Jaffe, S Bates

Romidepsin, an injectable histone deacetylase inhibitor, has demonstrated activity as a single agent in patients with cutaneous T-cell lymphoma (CTCL) in 2 previous phase II studies.[2,3] Based on these data, romidepsin has been approved by the US Food and Drug Administration (FDA) for the treatment of CTCL in patients who have received at least 1 prior systemic therapy.[4] In this phase II study, Piekarz and colleagues evaluated the efficacy and tolerability of romidepsin in the treatment of advanced peripheral T-cell lymphoma (PTCL). A total of 46 patients with relapsed or refractory PTCL who had received at least 1 prior standard chemotherapy regimen were enrolled. The patients received romidepsin 14 mg/m^2 as a 4-hr infusion on days 1, 8, and 15, every 28 days. Responses were assessed using elements of the International Working Group (IWG) criteria and Response Evaluation Criteria in Solid Tumors (RECIST), as appropriate, for patients with lymph node involvement and extranodal disease. The overall response rate (ORR) was 33% (11% complete response [CR]), and the overall median duration of response (DOR) was 9.0 months (range, 1.8 months–5.8 years). The median DOR for the 5 patients who achieved a CR was 6.0 months (range, 2.8 months–5.8 years). Among the 32 patients who had received at least 2 cycles of treatment, the ORR was 47% (16% CR).

The authors found that the drug was well-tolerated. The most frequent drug-related adverse events (AEs) were generally mild and included nausea (74%; 9% ≥grade 3), fatigue (72%; 20% ≥grade 3), decreased platelets (72%; 35% ≥grade 3), cardiovascular/general-other (72%; 0% ≥grade 3) and decreased absolute granulocyte count (AGC [65%; 43% ≥grade 3]. One death, in a patient with significant cardiovascular disease who had achieved a CR, was considered possibly related to treatment.

Based on the data, a phase IIb protocol investigating romidepsin in patients with relapsed or refractory PTCL is ongoing at multiple international centers.

1674 Pralatrexate and Gemcitabine in Patients with Relapsed or Refractory Lymphoproliferative Malignancies: Phase 1 Results[5]

SM Horwitz, JM Vose, R Advani, K Sankhala, S Padmanabhan, PA Hamlin Jr, A Chen, JM Zain, S Fruchtman, OA O'Connor

The antifolate agent pralatrexate and gemcitabine each have activity as monotherapy in patients with relapsed or refractory lymphoma. Preclinical data have reported increased efficacy when these agents are combined and tested in non-Hodgkin lymphoma cell lines and xenografts; this efficacy appears to be temporally dependent upon pralatrexate being followed by gemcitabine.[6] Horwitz and colleagues therefore conducted a multi-center phase I/IIa study (PDX-009; NCT00481871) to evaluate this treatment combination for patients with relapsed or refractory lymphoma. The primary objective of the phase I portion was to determine the maximum tolerated dose (MTD) and optimal phase II dose and schedule for the combination of pralatrexate and gemcitabine.

The eligibility criteria included histologically confirmed lymphoma, progressive disease after at least 1 prior treatment, and an Eastern Cooperative Oncology Group (ECOG) performance score of 2 or less. Prior gemcitabine exposure was permitted. As of May 2009, a total of 34 patients had been enrolled: 13 patients with B-cell lymphoma, 11 with T/NK-cell lymphoma, 7 with Hodgkin lymphoma, and 3 with other types of lymphoma. Patients had received a median of 3.5 prior regimens (range, 1–11). There were 3 treatment groups in this study. Patients in group A (n=7) received pralatrexate 10–15 mg/m^2 on day 1 and gemcitabine 300–400 mg/m^2 on day 2, once weekly for 3–4 weeks. Patients in group B (n=10) also received pralatrexate and gemcitabine on sequential days, but were treated only every 2 weeks. Patients in group C (n=17) received pralatrexate followed 1 hour later by gemcitabine, once every 2 weeks. All patients received vitamin B12 and folic acid supplementation.

All patients in group A had dose-limiting toxicities (DLTs) of thrombocytopenia and/or neutropenia, so accrual to this schedule was halted. The MTD with the dosing schedule of every 2 weeks was pralatrexate 10 mg/m^2 and gemcitabine 400 mg/m^2 when given on sequential days (group B) and pralatrexate 15 mg/m^2

Table 1. Summary of Response by Lymphoma Type

	Hodgkin Lymphoma n (%)	PTCL n (%)	B-cell Lymphoma n (%)
Partial Response	4 (57)	2 (18)	2* (13)
Stable Disease	2	2	2
Progressive Disease	1	7	11
Not Assessable	0	0	1

*Includes 1 patient with mixed B-cell and T-cell histology.
PTCL=peripheral T-cell lymphoma.

Table 2. Treatment and Dose Modifications for Toxicity

The scheduled pralatrexate dose was omitted when a patient experienced:
Platelets <50,000/uL
Absolute neutrophil count 500–1,000/uL with fever
Absolute neutrophil count <500/uL
Grade 2–4 mucositis
Any other grade 3 treatment-related event
The pralatrexate dose was reduced to 20 mg/m^2 when:
Platelets <25,000/uL on 2 occurrences
Recurrence of absolute neutrophil count 500–1,000/uL with fever
Recurrence of absolute neutrophil count <500/uL
Recurrences of grade 2 mucositis
Grade 3–4 mucositis
The patient experienced any grade 4 treatment-related event

and gemcitabine 600 mg/m^2 when given on the same day (group C). The DLTs for group B were cellulitis, pulmonary embolus, thrombocytopenia, and febrile neutropenia; the DLTs for group C were fatigue, hypoxia, mucositis, and thrombocytopenia. Across all groups, the most frequently reported grade 3/4 pralatrexate-related AEs were neutropenia (41%), thrombocytopenia (35%), anemia (29%), and leukopenia (12%). Of 33 patients who were evaluable for response, 21% achieved a partial response (PR). Table 1 shows the breakdown of response rates by lymphoma subtypes. Responses were seen in patients treated on the same day as well as the sequential day schedules.

Horwitz and colleagues concluded that combination treatment with pralatrexate and gemcitabine is feasible with acceptable toxicity when administered on an every-2-week schedule. However, the MTD of each drug is 50% greater when given on the same day as compared to treating on sequential days. Phase II expansion studies are under-way and will explore both sequential-day dosing (10 mg/m^2 and 400 mg/m^2) and same-day dosing (15 mg/m^2 and 600 mg/m^2) in an every-2-week schedule.

1675 Safety and Management of Pralatrexate Treatment in Relapsed or Refractory Peripheral T-Cell Lymphoma (PTCL)[7]

L Pinter-Brown, SM Horwitz, B Pro, PL Zinzani, C Gisselbrecht, BM Cortelli, S Fruchtman, OA O'Connor

Pralatrexate is a rationally designed antifolate that has a high affinity for reduced folate carrier-1 (RFC-1) and is an efficient substrate for polyglutamation by folylpolyglutamyl synthetase, resulting in increased drug uptake and retention by cells.[8] The PROPEL (Pralatrexate in patients with Relapsed Or refractory PEripheral T-cell Lymphoma) study[9] of pralatrexate in patients with relapsed or refractory PTCL found an ORR of 29% (32/109) by independent central review (11% CR/CR unconfirmed [CRu]). The median DOR was 10.1 months. Patients accrued to PROPEL had received a median of 3 prior therapies, and 68% had received combination chemotherapy or stem cell transplant just prior to inclusion in the study. In the present analysis, Pinter-Brown and colleagues assessed the safety profile of pralatrexate as seen in the PROPEL trial broken down according to duration of treatment. They also evaluated both early and late-onset toxicities and assessed the effect of dose modification upon the safety profile.

To be eligible to enroll in the PROPEL trial, patients were required to have PTCL histologically confirmed by central review, disease progression after at least 1 prior treatment, and an ECOG performance status of 2 or less. Response was assessed centrally using the International Workshop Criteria. A total of 111 patients received pralatrexate 30 mg/m^2 IV once weekly for 6 weeks in 7-week cycles with supplementation of vitamin B12 (1 mg IM every 8–10 weeks) and folic acid (1.0–1.25 mg orally daily). A dosing reduction schema was designed at the start of the trial (Table 2).

The investigators found that pralatrexate was well-tolerated overall. Patients received pralatrexate for a mean of 112 days (range, 1–558), and 19 patients received pralatrexate for at least 180 days, including 10 who received pralatrexate for at least 300 days. Sixty-four patients received 2 or more cycles of therapy, of which 43 patients received 3 or more cycles. The planned dosing intensity

was 25.7 mg/m^2/week, but the actual dosing intensity achieved in the trial was 20.6 mg/m^2/week. The most common AEs were mucosal inflammation (71%; 22% grade 3/4); nausea (41%; 4% grade 3); thrombocytopenia (41%; 33% grade 3/4); fatigue (36%; 7% grade 3/4); and anemia (34%; 18% grade 3/4). The incidence of grade 3/4 AEs decreased after the second cycle for patients who received 3 or more cycles. Dose modifications were necessary for 32% of the 111 patients in the study. The most common reason was mucosal inflammation (23%), followed by fatigue (2%), abnormal liver function test (2%), and thrombocytopenia (2%).

In conclusion, the authors found that pralatrexate was tolerable for patients with refractory and relapsed PTCL. They noted that the protocol-specified dose modification schema permitted continued therapy even after an occurrence of mucosal inflammation or other AEs, and that the drop in AE incidence after cycle 3 indicates the unlikelihood of cumulative-dose toxicity with pralatrexate.

1678 Pralatrexate Induces Responses in Patients with Highly Refractory Peripheral T-Cell Lymphoma (PTCL)[10]

KJ Savage, A Shustov, A Goy, SM Horwitz, B Pro, M Patterson, S Fruchtman, OA O'Connor

In this poster presentation, Savage and colleagues reported data from a second analysis of data from the PROPEL study[9] of pralatrexate in patients with relapsed or refractory PTCL. The objective of the analysis was to characterize the treatment response among patients who were considered to have highly refractory disease, defined as showing either no evidence of response to their most recent prior therapy or no evidence of response to all prior therapies. In the PROPEL trial, 111 patients received pralatrexate 30 mg/m^2 once weekly for 6 weeks in 7-week cycles, with vitamin B12 and folic acid supplementation. Patient response to pralatrexate was assessed after each odd-numbered treatment cycle and was based on centralized review of imaging and clinical data using the International Workshop Criteria.[11]

Of the 109 patients who were evaluable for response in PROPEL, 63% of patients had no evidence of response to their most recent therapy, and 24% of patients had no evidence of response to any therapy. Here, Savage and colleagues found that ORR for the 69 patients in the study with no evidence of response to their most recent prior therapy was 25% according to central review, and the median duration of response was 99 days (range, 41–535) by central review. The median number of prior systemic therapies for these 69 patients was 3 (range, 1–11). Among the 26 patients who had no evidence of response to any prior therapy before initiating pralatrexate, the ORR was 19%, with responses ranging in duration of 54–306 days. The safety profile of pralatrexate seen in this subanalysis was similar to that seen for the overall population of the PROPEL trial. The authors thus concluded that their data support the idea that pralatrexate can overcome mechanisms of drug resistance in patients with PTCL who were refractory to their most recent therapy, including patients who were refractory to all prior therapies.

1681 Correlation Between Baseline Methylmalonic Acid Status and Mucositis Severity in the PROPEL Study: Implications for Vitamin Prophylaxis[12]

B Pro, B Coiffier, SM Horwitz, A Boyd, E Neylon, S Fruchtman, OA O'Connor

Nutritional status is a concern for cancer patients in general, and particularly for patients with aggressive disease that have been treated previously. Prophylactic vitamin supplementation with folic acid and vitamin B12 is thus often used by physicians to minimize toxicities seen with antifolate chemotherapy, such as methotrexate or pralatrexate.[13] In the PROPEL study,[9] the most common grade 3/4 toxicities were thrombocytopenia (33%) and mucositis (22%). Pro and colleagues reported the results from their analysis of baseline methylmalonic acid (MMA), homocysteine (Hcy), and red blood cell (RBC) folate levels and their association with thrombocytopenia or mucositis in the PROPEL trial.

In PROPEL, 111 patients received pralatrexate 30 mg/m^2 IV weekly for 6 weeks in 7-week cycles and supplementation with vitamin B12 (1 mg IM every 8–10 weeks) and folic acid (1.0-1.25 mg orally daily). MMA, Hcy, and RBC folate were measured at baseline, prior to vitamin initiation. A linear model was used to estimate the relationship (slope) between each of these baseline values and the maximum grade of mucositis and thrombocytopenia. Pro and colleagues found that the linear relationship between maximum mucositis grade on study (0 vs 1–2 vs 3–4) and baseline MMA was statistically significant (slope estimate, 43.3 nmol/L; P=.039). In addition, there was a trend for increasing MMA and severity of thrombocytopenia that did not meet statistical significance (slope estimate, 17.6 µmol/L; P=.267). No significant relationships were found for Hcy or RBC folate.

The investigators noted that higher levels of baseline MMA were associated with increased severity of mucositis

in this analysis, prompting them to suggest that all patients treated with pralatrexate, especially those with elevated MMA, should be supplemented with vitamins. Additional studies appear warranted to further define the relationship between MMA levels and the development of mucositis and thrombocytopenia among pralatrexate-treated patients.

1709 The Systemic Effects of Vorinostat in Patients with Cutaneous T-Cell Lymphoma: Post-Hoc Analyses in Patients with High Blood Tumor Burden[14]

M Duvic, YH Kim, TM Kuzel, TR Pacheco, FM Foss, S Parker, S Rizvi, C Chen, JM Arduino, EA Olsen

CTCL patients with a high blood tumor burden have a poorer prognosis, making the development of treatment options for these patients a potent unmet medical need. Vorinostat is an oral histone deacetylase inhibitor that has been approved by the FDA for the treatment of cutaneous manifestations of CTCL in patients with progressive and persistent disease despite 2 prior systemic therapies.[15] A previous open-label, phase IIb study published in 2007 found that vorinostat was well tolerated and associated with an ORR of 29.7%. Of note, patients with stage IIb disease or greater exhibited a similar response rate of 29.5%.[16] Here, Duvic and colleagues conducted a post hoc analysis of the phase IIb study data in order to assess the potential efficacy of vorinostat for the treatment of systemic CTCL in patients with high blood tumor burden.

In the phase IIb study, patients with advanced CTCL received oral vorinostat 400 mg daily until disease progression or intolerable toxicity. Study patients had received at least 2 prior systemic therapies that included bexarotene unless it was intolerable. A high blood tumor burden was defined as a baseline CD4+/CD26- cell count of greater than 1,000/µL by flow cytometry. Patients with Sézary syndrome (SS) were also required to have greater than 80% erythroderma at the time of study entry. The tumor responses in the blood and skin were examined. An objective blood response was defined as at least a 50% decrease in blood tumor burden and progression as at least a 25% increase from baseline. An objective response in the skin was defined as at least a 50% reduction in modified Severity-Weighted Assessment Tool (mSWAT) score from baseline.

Of 74 patients who entered the phase IIb trial, 18 had a high blood tumor burden and were included in the post hoc analysis. Of these 18, SS was present in 11 patients. The authors found that vorinostat treatment showed promising efficacy in this analysis. An objective blood response was observed in 28% of patients and an objective skin response was observed in 44%. An objective response in both blood and skin was observed in 17%. For the 11 patients with SS in the analysis, the median change in blood tumor burden was a 35% decrease, while the median change in blood tumor burden for the 7 patients not meeting criteria for SS was a 39% decrease. Therefore, Duvic and colleagues concluded that vorinostat may be effective for the reduction of both skin and blood tumor burden in patients with CTCL and SS.

1710 The Combined Safety and Tolerability Profile of Vorinostat-Based Therapy for Solid or Hematologic Malignancies[17]

D Siegel, PN Munster, E Rubin, M Iwamoto, S van Belle, M Hussein, CP Belani, F Robert, E Galanis, J Hardwick, S Rizvi

Vorinostat is approved in the United States for the treatment of cutaneous manifestations of CTCL in patients who have progressive, persistent, or recurrent disease on or following 2 systemic therapies.[15] In addition, vorinostat is also being investigated as a treatment for various other solid and hematologic malignancies. Whether or not treatment with vorinostat increases the QTcF interval or raises the risk of thromboembolic events (TEE) has been the subject of much interest. Therefore, in this study, Siegel and colleagues presented an overview of the safety and tolerability data gathered from phase I and II clinical trials of vorinostat for solid or hematologic malignancies. Data from a phase II trial investigating the effect of vorinostat upon the QTcF interval were also presented.

Data from 498 patients who received vorinostat, either as a monotherapy or as a combination therapy, were analyzed. Among the 341 patients who received vorinostat monotherapy, 107 had CTCL, 105 had other hematologic malignancies, and 129 had solid tumors. The most common drug-related AEs in the monotherapy group were fatigue (61.9%), nausea (55.7%), diarrhea (49.3%), anorexia (48.1%), and vomiting (32.8%). Grade 3/4 AEs included fatigue (12.0%) and thrombocytopenia (10.6%), and 3 drug-related deaths (ischemic stroke, tumor hemorrhage, unspecified) occurred. Thirty-eight patients (11.1%) discontinued treatment due to drug-related AEs; 71 patients (20.8%) required dose modifications, and 1 patient (0.3%) discontinued due to grade 2 chest pain.

The remaining 157 patients received vorinostat combination therapy as follows: with pemetrexed/cisplatin for advanced cancer (n=46); with bortezomib for multiple myeloma (n=34); with bexarotene for CTCL (n=23); and

with erlotinib (n=30), gemcitabine/platin (n=21), or carboplatin/paclitaxel (n=3) for non–small-cell lung cancer. The most common drug-related AEs in this group were nausea (48.4%), diarrhea (40.8%), fatigue (34.4%), and vomiting (31.2%). The most common grade 3/4 AE was fatigue (13.4%). One drug-related death (hemoptysis) occurred. Thirty-one patients (19.7%) discontinued treatment due to drug-related AEs, and 27 patients (17.2%) required dose modifications.

In addition to the AE overview, a review of vorinostat clinical trials, published literature, and postmarketing surveillance reports was conducted by a committee of independent academic experts to determine the incidence of TEE in cancer patients who had received vorinostat. Data from 1,845 patients were reviewed. A total of 107 cases of serious TEE occurred, 47 (<2.6%) of which were recorded as being related to vorinostat. Of these 47 cases, 4 (<0.3%) were fatal.

Lastly, a trial of vorinostat in 24 patients with advanced cancer was undertaken for rigorous assessment of QTcF interval. In this trial, a single supratherapeutic 800 mg dose of vorinostat did not prolong QTcF interval as monitored over 24 hours. The upper limit of the 90% confidence interval for the placebo-adjusted mean change-from-baseline of vorinostat was less than 10 msec at every timepoint. No patient had a QTcF change-from-baseline value over 30 msec. The most common drug-related AE in this trial was nausea. There were no serious clinical or laboratory AEs, no discontinuations due to an AE, and no patients experienced a cardiac-related AE.

The authors concluded that vorinostat is generally well-tolerated when administered as monotherapy or in a combination regimen in cancer patients, does not appear to prolong the QTcF interval, and does not appear to significantly raise the incidence of TEE over the level reported in general advanced cancer patients.

2683 Clinically Significant Responses Achieved with Romidepsin in 37 Patient with Cutaneous T-Cell Lymphoma (CTCL) with Blood Involvement[18]

YH Kim, M Demierre, EJ Kim, AH Rook, A Lerner, M Duvic, S Reddy, T Robak, JC Becker, A Samtsov, W McCulloch, S Whittaker

Romidepsin is an injectable histone deacetylase inhibitor that has been approved by the FDA for the treatment of CTCL in patients who have received at least 1 prior systemic therapy.[4] This approval was based in part upon the data from an open-label, international phase II study presented by Kim and colleagues at the 2008 meeting of the American Society of Hematology.[2] In that study, the ORR among 96 patients was 34%, including 6 CRs. The median DOR was 14.9 months. Here, efficacy data from 27 study patients whose disease had blood involvement were presented, showing a clinical benefit with romidepsin for this population.

Eligible patients had failed at least 1 prior systemic therapy, had adequate organ function, and had an ECOG performance status of 0 or 1. Patients received romidepsin 14 mg/m^2 as a 4-hour IV infusion on days 1, 8, and 15 every 28 days for up to 6 cycles, which could be extended for stable disease (SD) or response. Of the 96 patients in the original phase II study, 37 patients had greater than 5% circulating Sézary cells. Of these, 27 patients had also received at least 2 cycles of romidepsin. Among these 27 patients, the ORR was 32% by composite assessment, including 2 CRs. The median DOR had not been reached; the maximum DOR was 19.8 months.

The safety profile of romidepsin in the subanalysis was similar to the overall safety profile of romidepsin. The investigators did not observe any unusual drug-related AEs. They concluded that romidepsin treatment offers clinical benefit to heavily pretreated patients with CTCL with blood involvement.

3745 Complete Responses with Denileukin Diftitox in Cutaneous T-Cell Lymphoma Studies[19]

F Foss, M Duvic, EA Olsen, A Kozlovski

Denileukin diftitox is a recombinant fusion protein combining interleukin-2 (IL-2) and diphtheria toxin. It binds to the CD25 component of the IL-2 receptor, prompting cells to internalize the drug. Diphtheria toxin is thus introduced into the cytosol of targeted cells, where it inhibits protein synthesis, leading to cell death.[20] Denileukin diftitox has been approved by the FDA for the treatment of patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor.[21] The objective of this post-hoc study by Foss and colleagues was to analyze the data from 3 previously conducted phase III trials of denileukin diftitox in order to determine if dose level or CD25 status were statistically associated with differences in response rate, DOR, or progression-free survival (PFS).

The first of the 3 studies that provided data for this analysis was study 93-04-10.[22] This study was a blinded, multicenter trial of denileukin diftitox in 71 CTCL patients with CD25-positive disease who had received at least 4 prior therapies for stage Ib–III disease or at least 1 previous therapy for stage IVa disease. The patients were

Table 3. Median Duration of Response and Progression-free Survival

Median Duration of Response					
	CD25 positive			**CD25 negative**	
	9 µg/kg/day DD naïve (N=6)	18 µg/kg/day DD naïve (N=13)	18 µg/kg/day Re-treated (N=2)	18 µg/kg/day DD naïve (N=3)	All DD treated (N=24)
Median Duration of Response (Days)	>1325	>1247	180	>400	>1325
Progression-free Survival					
	CD25 positive			**CD25 negative**	
	9 µg/kg/day DD naïve (N=6)	18 µg/kg/day DD naïve (N=13)	18 µg/kg/day Re-treated (N=2)	18 µg/kg/day DD naïve (N=3)	All DD treated (N=24)
Median PFS (Days)	>1388	>1286	309	>487	>1388

DD=denileukin difitox

randomized 1:1 to receive denileukin diftitox 9 µg/kg/day or 18 µg/kg/day on days 1 to 5 of each 21-day course, for up to 8 courses. The ORR in this study was 30% (10% CR). Broken down by dosing group, the response rates were 23% and 36% for patients treated with 9 µg/kg/day and 18 µg/kg/day, respectively, which was not a statistically significant difference.

The second study was 93-04-11, a double-blind, placebo-controlled, multicenter trial designed to confirm the results of 93-04-10 in a less heavily pretreated population.[21] Patients in this trial had recurrent or persistent stage Ia–III disease that had been biopsy-documented to express CD25 and had failed no more than 3 previous therapies. A total of 144 patients were randomized to receive either denileukin diftitox 9 µg/kg/day (n=50), 18 µg/kg/day (n=50), or placebo (n=44). The ORR for both treatment arms was 44%. Broken down by dosing group, the response rate was 38% for the high-dose arm and 49% for the low-dose arm, compared with only 16% for placebo. Ten patients achieved a CR in this study. The median PFS was 971 days in the high-dose arm, 794 days in the low-dose arm, and 124 days in the placebo group (P=.0024 low-dose vs placebo; P<.0001 high-dose vs placebo).

The third study was 93-04-14, an open-label rollover study[23] that included patients from 4 groups: 1) patients on protocol 93-04-11 who were randomized to a denileukin diftitox arm and experienced SD through 8 courses, 2) patients on protocol 93-04-11 who were randomized to placebo and experienced SD through 8 courses, 3) patients who relapsed during follow-up after an initial response to denileukin diftitox on protocol 93-04-11, or 4) patients who were excluded from protocol 93-04-11 only because their disease tested CD25-negative. The ORR in this rollover study was 59% in the placebo cross-over patients, 40% in the relapsed and retreated patients, and 31% in CD25-negative patients. These differences were not statistically significant. Eleven patients had a CR.

In this post-hoc analysis, Foss and colleagues examined the data from the 263 intent-to-treat patients in these 3 phase III trials. Of these patients, 227 had CD25-positive skin infiltrates by immunohistochemistry as confirmed by a reference pathologist, and 36 had CD25-negative disease. Overall, 24 (9.1%) patients attained durable CR, and the CR rate was similar between the early and advanced stage patients (10.7% vs 8.9%). The CR rate did not differ significantly between the 9 and 18 µg/kg denileukin diftitox groups (P=.56) nor between the CD25-positive (n=118) and CD25-negative (n=36) groups (P=.64). The authors pointed out, however, that the number of CD25-negative patients was small in this analysis.

The DOR and PFS differed between groups (Table 3). The DOR ranged from 57 days to more than 1,325 days in the CD25-positive groups, and from 190 to 400 days in the CD25-negative group. The overall median PFS at the time of analysis had not been reached (range, 169–1388 days). The authors concluded that the studies demonstrate clinical benefit with denileukin diftitox in both early and advanced CTCL at both the 9 µg/kg and 18 µg/kg doses, producing durable CRs in a small number of patients.

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Commentary

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The present standards of care for the treatment of peripheral T-cell lymphoma (PTCL) are woefully inadequate. Many of the treatments now used for PTCL are basically taken from our experiences in B-cell lymphoma. As a result, combination chemotherapy regimens like CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) have become the de facto standard. While many physicians who care for patients with PTCL openly acknowledge the suboptimal results with standard CHOP-based chemotherapy, there are no data nor a consensus regarding the most suitable alternatives. The lack of consensus is underscored in the recent National Comprehensive Cancer Network (NCCN) guidelines, which recognizes no "standard of care," and in fact, suggests enrollment in clinical trials as the recommended treatment for patients in both the frontline and beyond. This conundrum frustrates both physicians and patients alike, underscoring the urgent need for new treatments and some accepted standards of care beyond investigational therapy.

Fortunately, over the last several years, there has been an enormous increase in the number of new agents and new strategies becoming available for the treatment of patients with PTCL. In the frontline, there have been emerging data that suggest that autologous stem cell transplant (ASCT) in first remission may be one of the more effective treatments for these patients, assuming that patients can attain significant responses with CHOP-based therapy. Respectable long-term survival for those patients who attain complete remission has been reported (71% at 3 years),[1] in contrast to those who do not receive an ASCT in first remission (3-year survival, 11%). Regrettably, 34% of all patients treated with a standard CHOP-like therapy could not advance to ASCT due to the nature of their poor response. In the relapsed and refractory setting, there are many more questions. Patients who experience a relapse of their disease may have some alternative treatment ranging from combination chemotherapy (EPOCH [cyclophosphamide, doxorubicin, etoposide, prednisone, vincristine], gemcitabine-based combinations, or ICE [carboplatin, etoposide, ifosfamide]) to single-agent treatments with agents like gemcitabine alone, oral etoposide, denileukin diftitox, and most recently, pralatrexate.

In September 2009, pralatrexate became the first drug to be approved for the treatment of relapsed or refractory PTCL. Pralatrexate is a novel antifolate designed to have high affinity for the reduced folate carrier, and is thus more efficiently internalized and polyglutamylated by folylpolyglutamyl synthase (FPGS). The polyglutamylated derivatives of pralatrexate, similar to those of methotrexate, then inhibit dihydrofolate reductase. In preclinical studies, pralatrexate is at least a log more potent than other antiofolates like methotrexate, and in in vivo models of B- and T-cell lymphoma, it is markedly superior to methotrexate. An early phase "II-I-II" experience in patients with drug resistant B-cell lymphoma suggested that supplementation with folic acid and vitamin B12 could ameliorate much of the mucositis that was previously seen with the agent in solid tumor phase I clinical trials, and that dosing on a weekly schedule produced higher areas under the curve of exposure (AUC), likely contributing to the lesser risk of mucositis and improved efficacy.[2,3] In fact, in the weekly phase II study early on, complete and partial remissions were seen across many subtypes of PTCL with durable responses.

These observations gave rise to the pivotal study PROPEL (Pralatrexate in patients with Relapsed Or refractory PEripheral T-cell Lymphoma), which was an international multicenter clinical trial of pralatrexate in patients with relapsed or refractory PTCL.[4] The patients treated in PROPEL were very heavily pretreated, with a mean of 3 prior therapies; more than 20% of patients had received more than 5 lines of prior treatment. The overall response rate in PROPEL was 29%, with a median duration of response of approximately 10 months. Of note, 25% of patients in PROPEL had primary refractory disease, and more than 50% of patients failed to respond to the line of chemotherapy immediately prior to study entry. One of the more important observations from the PROPEL study was based on a subset analysis of response as a function of different diagnostic or prognostic categories. Importantly, there was no statistically significant difference in response in patients who had 1–2 versus more than 5 prior lines of treatment; ASCT versus no ASCT; prior methotrexate versus no prior methotrexate; or according to age, gender, or histologic subtype. The only area where a difference was appreciated was in the response rate for angioimmunoblastic T-cell lymphoma (AITL), where only 1 of 13 patients responded. Though the numbers are small, the data did suggest that AITL may be more resistant to pralatrexate than other subtypes of PTCL.

Of course, the next step in the development of any new drug is to think about combinations. Based on preclinical studies both in vivo and in vitro, pralatrexate was found to be highly synergistic with gemcitabine (fortunately!) in a schedule-dependent manner. These data demonstrated that pralatrexate followed by gemcitabine was significantly more potent than either drug alone or when the drugs were given simultaneously. The schedule-dependent cytotoxicity of these agents was found to induce both caspase activation and apoptosis at a fraction of the EC50.

These observations led to the design of a phase I clinical trial, the data of which were presented at the 2009 meeting of the American Society of Hematology (ASH) by Dr. Steven Horwitz. This trial demonstrated that the maximum tolerated dose (MTD) of pralatrexate and gemcitabine when given on a day 1, 2 schedule was 10 mg/m^2 and 400 mg/m^2, respectively, and 15 mg/m^2 and 600 mg/m^2 when administered on the same day separated by 2–4 hours. The major dose-limiting toxicities were as expected and primarily included thrombocytopenia and neutropenia. Interestingly, however, significant response were seen in patients with Hodgkin lymphoma (4 of 7), PTCL (2 of 11), and B-cell lymphoma (2 of 16). Based on these data, the study has now moved into its phase II component where it will assess efficacy in both schedules.

In addition to nucleoside analogs, it is now also clear that pralatrexate synergizes with a number of other drugs known to be active in PTCL, including bortezomib and histone deacetylase (HDAC) inhibitors. Bortezomib, a proteasome inhibitor that has been approved for the treatment of multiple myeloma and mantle cell lymphoma, has been shown by Zinzani and colleagues to be very active in patients with both cutaneous T-cell lymphoma (CTCL) and PTCL, though the number of patients in this phase II study are limited. Preclinical models have documented marked synergy between pralatrexate and bortezomib in models of CTCL and T-cell acute lymphoblastic leukemia (T-ALL),[5] data which have formed the basis for a planned phase I-II clinical trial.

Perhaps one class of drugs with the most reproducible activity in T-cell lymphoma is the HDAC inhibitors. For reasons that are not entirely clear, there appears to be a class effect of these agents in T-cell malignancies and a very similar adverse event profile as well. The first HDAC inhibitor approved in T-cell lymphoma was vorinostat, which was approved for the treatment of relapsed or refractory CTCL. Interestingly, early phase I clinical trials[6,7] demonstrated that vorinostat could abrogate the pruritis associated with Hodgkin lymphoma and produced durable remissions in patients with relapsed and transformed lymphoma and Hodgkin lymphoma. In addition, correlative assays demonstrated that we could achieve a relatively high level of acetylated H3 (histone 3) accumulation following the exposure to vorinostat, but that demonstration of Ac-H3 did not correlate with response. In fact, one patient with relapsed PTCL who had a pre- and post-vorinostat biopsy exhibited marked accumulation of Ac-H3 in the tumor tissue proper, but did not achieve response. Based on this experience and the findings that other HDAC inhibitors such as depsipeptide (now known as romidepsin) were producing responses in patients with heavily treated T-cell lymphoma, a pivotal study of vorinostat was conducted in CTCL.[8,9] This experience suggested that vorinostat produced an overall response rate of approximately 29%, with an approximately 6-month duration of response. Vorinostat, originally studied in both intravenous and oral formulations, became the first HDAC inhibitor approved for the treatment of any cancer.

As a follow-up to these studies, Duvic and colleagues presented data at the 2009 ASH meeting on their original set of patients with CTCL, trying to characterize the benefit of vorinostat in CTCL patients with a high blood tumor burden. They defined a high tumor blood burden as a baseline CD4+/CD26- cell count greater than 1,000/ L by flow cytometry. Of 74 patients who entered the phase Ib study, 18 had a high blood tumor burden, of whom 11 had Sezary syndrome. The authors reported that the objective response in the blood was 28%, a rate nearly identical to the ORR, which was associated with an objective skin response rate of 44%, allowing the authors to conclude that vorinostat was active for both skin- and blood- compartmentalized disease.

While the HDAC inhibitors are commonly accepted as "safe agents," there has been some question revolving around potential class effects with regard to increases in QTc and thromboembolic events. Siegel and colleagues presented at ASH the results of 498 patients who received vorinostat as monotherapy or as combination therapy, in both solid tumor and hematologic patients. The most common adverse events were as expected, including fatigue, nausea, diarrhea, and anorexia. But one aspect of the study included an analysis of 24 patients who underwent rigorous EKG monitoring for prolongation of the QTc following a single 800 mg dose of vorinostat. No patient experienced a QTc change from baseline of more than 30 msec, and there were no other cardiac-related AEs. In keeping with the general experience of most physicians, the authors concluded that the primary toxicities associated with vorinostat were constitutional, and that there was no evidence of QTc prolongation, nor any increase in thromboembolic events.

In addition to vorinostat, romidepsin has emerged as having significant activity in T-cell lymphomas. Romidepsin is one of the most potent HDAC inhibitors developed to

date, having been recently granted full regulatory approval by the U.S. Food and Drug Administration (FDA) for the treatment of relapsed or refractory CTCL. This approval is based on pooled data obtained from an National Cancer Institute (NCI)–directed phase II trial of romidepsin in CTCL and a registration-directed trial by Gloucester Pharmaceuticals. This pooled analysis reported a response rate of 41% with a duration of response of approximately 14 months.[10] Other HDAC inhibitors presently in clinical trials include bellinostat and panobinostat, both of which have demonstrated promising activity in T-cell lymphomas.

Richard Piekarz, on behalf of his colleagues at the NCI, presented the final results of a phase II NCI multicenter study of romidepsin in patients with relapsed or refractory PTCL. These patients were treated with romidepsin at a dose of 14 mg/m^2 on a 4-hour infusion on days 1, 8, and 15 on an every-28-day cycle. The ORR from Dr. Piekarz's final results was 33% with 11% complete remission and an overall median duration of response of 9 months. Interestingly, the median duration of response for the 5 patients who achieved CR was 6 months. We anticipate that sometime this year, we should hear at least the preliminary results for the registration-directed study for patients with relapsed or refractory PTCL.

Clearly, the holy grail in lymphoma therapy these days seems to be striving toward the same successful paradigm developed in B-cell lymphoma, namely immunochemotherapy (as in rituximab-CHOP–based chemotherapy). Unfortunately, while there are many potential candidates on the horizon, it has been difficult to identify one antigen that is uniformly expressed on all T-cell malignancies alike; many of them exhibit only restricted expression. Targets including CD52, CD4, CCR4, and CD25 have potential monoclonal antibodies such as alemtuzumab, CD4 MAB, CCR4 MAB, and denileukin diftitox, respectively. While there has been some experience looking at the integration of denileukin diftitox into standard CHOP-based therapy, which seems to suggest some improvement in ORR and possibly PFS, there is no randomized data upon which we can definitively conclude that this MAB is our path to that immunochemotherapy platform. As we await these studies, single-agent studies of denileukin diftitox continue to emerge. In fact, in one such study presented at the 2009 ASH meeting, Foss and colleagues analyzed the data from 263 intent-to-treat patients who were enrolled in 3 phase III trials. Overall, of these 263 patients, 277 had CD25+ disease, while 36 had CD25- disease. A comparison of the duration of response among those naïve patients who were CD25+ treated with 9 mg/kg/day or 18 mg/kg/day was 1325 and 1247 days, respectively, while that of the CD25- patient cohort treated with 18 mg/kg/day was more than 400 days. A similar trend was noted in patients with CD25+ disease in PFS. The authors concluded that the clinical benefit of denileukin difitox was marked at both dose levels in patients with advanced and early disease, with an obvious trend toward improved benefit in those patients with expression of CD25.

While only a modest representation of the data was presented in 2009 on new agents in PTCL, it is clear that this disease is now getting its long overdue attention. With our successes, however, will come many challenges. First is the need to better understand the underlying molecular pathogenesis of this disease, so we can begin to formulate more rational therapeutic interventions. Secondly, there is the challenge of thinking about combination studies earlier, and then developing the appropriate preclinical evidence in support of one study over another. The rarity of PTCL will make our need to prioritize new studies imperative. As these advances with single agents mature and our understanding of how to combine these drugs in a rational manner evolves, it will be important to think about how we can develop new treatment platforms that will one day challenge the conventional CHOP-based treatments we so commonly employ. Until then, I think it is best to follow the recommendations of our colleagues at the NCCN and to enroll patients in clinical trials whenever possible.

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Notes

Recent Advances in the Treatment of T-cell Lymphomas

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

1. Which of the following agents is a rationally designed antifolate?

   a. pralatrexate
   b. vorinostat
   c. denileukin diftitox
   d. romidepsin

2. Which of the following agents binds to the IL-2 receptor?

   a. pralatrexate
   b. vorinostat
   c. denileukin diftitox
   d. romidepsin

3. In the phase II study of romidepsin in patients with relapsed or refractory PTCL presented by Piekarz and colleagues, the ORR was ___% and the median DOR was ___ months.

   a. 11% and 3.7 months
   b. 29% and 11.0 months
   c. 33% and 9.0 months
   d. 35% and 5.2 months

4. Horwitz and colleagues conducted a phase I/IIa study of combination treatment with pralatrexate and gemcitabine for patients with relapsed or refractory lymphoma. They found that the MTD of each drug is ____% greater when the drugs are given on the same day as compared to treating on sequential days.

   a. 25%
   b. 33%
   c. 45%
   d. 50%

5. In the analysis of the PROPEL data conducted by Savage and colleagues, an ORR of ___% was seen among the 26 patients who had had no evidence of response to any prior therapy before initiating pralatrexate.

   a. 9%
   b. 19%
   c. 29%
   d. 39%

6. In the analysis of the PROPEL data conducted by Pro and colleagues, an increased level of which of the following values at baseline was associated with an increased incidence of mucosal inflammation?

   a. Methylmalonic acid (MMA)
   b. Homocysteine (Hcy)
   c. Red blood cell folate
   d. All of the above

7. In the post-hoc analysis of phase IIb trial data from 18 patients with CTCL and a high blood tumor burden, Duvic and colleagues observed an objective blood response in ___% of patients and an objective skin response in ___%.

   a. 28% and 44%
   b. 33% and 28%
   c. 39% and 25%
   d. 15% and 11%

8. TRUE OR FALSE? In the trial presented by Siegel and colleagues testing the effect of vorinostat upon QTcF interval in 24 patients with advanced cancer, the authors found that a single supratherapeutic 800 mg dose of vorinostat significantly prolonged the QTcF interval as monitored over 24 hours.

   a. True
   b. False

9. In the post-hoc analysis by Kim and colleagues, romidepsin treatment produced an ORR of ___% among 27 patients with heavily pre-treated CTCL with blood involvement.

   a. 7%
   b. 12%
   c. 22%
   d. 32%

10. TRUE OR FALSE? In the post-hoc analysis by Foss and colleagues, the CR rate did not differ significantly between the 9 and 18 µg/kg denileukin diftitox groups.

    a. True
    b. False

Evaluation Form Recent Advances in the Treatment of T-cell Lymphomas

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
(1 = Strongly Disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly Agree)

1. Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Describe the importance of new study findings in the form of selected abstracts/poster summaries from ASH 2009 in the natural history of T-Cell Lymphoma. 1 2 3 4 5
2. Assess the results of these new study findings including current clinical trials evaluating therapy in the treatment of T-Cell Lymphoma. 1 2 3 4 5
3. Integrate into clinical practice the latest knowledge and methods for treating patients with T-Cell Lymphoma. 1 2 3 4 5
4. Identify future research directions for all therapies in T-Cell Lymphoma. 1 2 3 4 5

2. Overall Effectiveness of the Activity

The content presented:

- Was timely and will influence how I practice 1 2 3 4 5
- Enhanced my current knowledge base 1 2 3 4 5
- Addressed my most pressing questions 1 2 3 4 5
- Provided new ideas or information I expect to use 1 2 3 4 5
- Addressed competencies identified by my specialty 1 2 3 4 5
- Avoided commercial bias or influence 1 2 3 4 5

3. Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity: _____

Please list any topics you would like to see addressed in future educational activities: _____

_____

Additional comments about this activity: _____

_____

4. Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I'm not interested in participating in a follow-up survey.

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