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Advances in the Treatment of T-cell Lymphomas

Review of Presentations at

- American Society of Clinical Oncology
  Annual Meeting
  May 29–June 2, 2009
  Orlando, Florida
- Pan Pacific Lymphoma Conference
  June 22–26, 2009
  Kohala Coast, Hawaii

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This activity has been designed to meet the educational needs of hematologist and oncologists involved in the management of patients with T-cell lymphoma.

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:

- Describe the importance of new study findings in the form of selected abstracts/poster summaries in the natural history of T-cell lymphomas
- Cite the results of these new study findings including current clinical trials evaluating therapy in the treatment of T-cell lymphomas
- Explain into clinical practice the latest knowledge and methods for treating patients with T-cell lymphomas in an effort to improve current prognosis statistics
- Identify future research directions for all therapies in T-cell lymphomas.

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8500 Complete Remissions With Weekly Dosing of SGN-35, a Novel Antibody-Drug Conjugate Targeting CD30, in a Phase I Dose-escalation Study in Patients With Relapsed or Refractory Hodgkin lymphoma or Systemic Anaplastic Large Cell Lymphoma[1]

N Bartlett, A Forero-Torres, J Rosenblatt, M Fanale, SJ Horning, S Thompson, EL Sievers, DA Kennedy

SGN-35, also known as brentuximab vedotin, is an antibody-drug conjugate comprising a chimeric anti-CD30 antibody attached to the synthetic tubulin inhibitor monomethyl auristatin E (MMAE).[2] SGN-35 releases MMAE upon internalization into CD30-expressing tumor cells, resulting in cell-cycle arrest and apoptosis. An earlier phase I study of SGN-35 demonstrated an objective response rate of 54% at doses of 1.2 mg/kg or higher in patients with Hodgkin lymphoma or systemic anaplastic large cell lymphoma (ALCL), an indolent NHL that affects T cells, diseases characterized by CD30-expressing tumor cells.[3] As a result, a dose-escalation phase I trial was designed to determine if antitumor activity could be maximized with a more frequent dosing schedule. Patients with recurrent or refractory Hodgkin lymphoma or systemic ALCL were administered weekly 2-hour intravenous infusions of SGN-35 at doses of 0.4–1 mg/kg. Patients who achieved stable disease or better after 2 28-day cycles of 6 doses were eligible to continue treatment with SGN-35. The trial enrolled 17 patients (median age, 38 years; range, 25–67) who had received a median of 4 prior therapies, with 65% having undergone autologous stem-cell transplantation. The most common adverse events (AEs) were grade 1/2 rash, nausea, and peripheral neuropathy; grade 3 diarrhea was reported in 1 patient. The maximum tolerated dose was not defined. One patient with systemic ALCL achieved stable disease at 0.4 mg/kg; 1 achieved complete remission (CR) at 0.8 mg/kg, and 2 achieved CR at 1.0 mg/kg. Patients with Hodgkin lymphoma also achieved CR at the higher dose levels. The time to response was approximately 8 weeks at the 1 mg/kg dose level. Of the 7 patients who achieved CR, all remain on therapy. In this heavily pretreated population, SGN-35 was considered to be generally well-tolerated and efficacious at the highest dose levels.

8524 Activity of Lenalidomide in a Phase II Trial for T-cell Lymphoma: Report on the First 24 Cases[4]

GS Dueck, N Chua, A Prasad, D Stewart, D White, R van der Jagt, JB Johnston, A Belch, T Reiman

Lenalidomide, an immunomodulatory agent approved by the U.S. Food and Drug Administration for the treatment of multiple myeloma[5] and 5q- myelodysplastic syndromes,[6] was investigated as monotherapy in 24 patients with relapsed and refractory T-cell lymphomas other than mycosis fungoides. In this phase II trial, lenalidomide was administered orally at a daily dose of 25 mg on days 1–21 of a 28-day cycle, with standardized dose reductions for toxicity as needed. The 2-stage trial design includes

a primary endpoint of overall response rate (ORR) and secondary endpoints of CR and partial response (PR) rates, progression-free survival (PFS) and overall survival, and safety. Treatment was continued until death, progression, or unacceptable levels of toxicity. The patients (median age, 65 years) had Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 (n=15), 2 (n=7), or 3 (n=2). Histologic assessment showed peripheral T-cell lymphoma unspecified (PTCL-u; n=10), angioimmunoblastic lymphoma (n=7), ALCL (n=5), enteropathic T-cell lymphoma (n=1), and hepatosplenic gamma/delta T-cell lymphoma (n=1). Patients had a median of 1 prior therapy (range, 0–4), and 3 patients previously underwent autologous stem-cell transplantation. The median time from completion of previous therapy was 8 months (range, 1–48 months). Four patients were previously untreated but were not considered to be candidates for standard combination chemotherapy. Dr. Dueck and colleagues reported that of 23 patients evaluable for response at the time of the interim analysis, the ORR was 30% (7 of 23 patients, all with PR), with a median PFS of 96 days (range, 8–696 days). Stable disease was achieved in 2 patients for at least 3 cycles. Patients with PTCL-u, angioimmunoblastic, and anaplastic histologies experienced responses. The median overall survival was 241 days (range, 8–696). Among those patients who achieved outcomes of stable disease or better (n=9), median PFS was 168 days and median overall survival had not been reached with 241–696 days of follow-up. Thrombocytopenia was the most common grade 4 AE, seen in one third of patients. Neutropenia (20.8%), febrile neutropenia (16.7%), and unspecified pain (16.7%) comprised the most common grade 3 AEs. Dr. Dueck and colleagues concluded that the administration of lenalidomide in this cohort achieved the expected results, concordant with the experience in other disease states. Further investigation is thus warranted.

8546 Pooled Analyses of Two International, Multicenter Clinical Studies of Romidepsin in 167 patients With Cutaneous T-cell Lymphoma[7]

M Demierre, S Whittaker, Y Kim, E Kim, R Piekarz, M Prince, J Nichols, J Balser, A Prentice, S Bates

The histone deacetylase (HDAC) inhibitor romidepsin has demonstrated clinical activity in patients with Sézary syndrome and mycosis fungoides.[8,9] Data from the pivotal study[10] and a supporting study[11] were pooled for further analysis. The pivotal study (GPI-04-0001) enrolled 96 patients with cutaneous T-cell lymphoma (CTCL) who had received at least 1 prior treatment (median, 2; range, 1–8); the supporting study (NCI 1312) enrolled 71 patients with CTCL who had received at least 1 prior treatment (median, 3.4; range, 1–10). In both studies, patients received romidepsin at a dose of 14 mg/m^2 as a 4-hour infusion on days 1, 8, and 15 of a 28-day cycle until disease progression. Both studies' primary efficacy endpoint was ORR composed of skin assessment, lymph node and visceral involvement, and abnormal circulating T/Sézary cells. Of a total of 167 patients, 135 (mean age, 57 years) were in the efficacy-evaluable population. The ORR was 41% (n=55; Table 1). It was noted that 42% of patients with stage IIB or greater disease experienced responses. Twenty of 52 (38%), and 8 of 20 (40%) patients who previously received bexarotene and denileukin diftitox, respectively, achieved responses. The most common drug-related AEs, regardless of grade, were nausea (67%), fatigue (49%), anorexia (37%), electocardiogram T-wave changes (29%), anemia (26%), dysgeusia (23%), neutropenia (22%), and leukocytopenia (20%). Serious AEs that occurred in 2% of patients included supraventricular arrhythmia, ventricular arrhythmia, infection, neutropenia, decreased white blood cell count, hyperuricemia, and hypotension. Three deaths were reported as possibly related. The researchers concluded that the pooled analysis supported previously reported results, with romidepsin found to be associated with positive outcomes across disease stages and among various subpopulations.

Table 1. Efficacy Findings, Pooled Analysis of GPI-040-0001 and NCI 1312: Romidepsin in Previously Treated Patients with CTCL

Efficacy Parameter	Evaluable Patients* (N=135)
Overall response, n (%)	55 (41%)
Complete response, n (%)	10 (7%)
Partial response, n (%)	45 (33%)
Median duration of response, months	14.9 (range, 1–66)
Median time to disease progression, months	8.3 (range, 1–70)

* Patients who received ≥2 cycles.

8549 Phase I/II Study of Concurrent Chemoradiotherapy for Localized Nasal NK/T-cell Lymphoma: Final Results of JCOG0211[12]

M Yamaguchi, K Tobinai, M Oguchi, Y Isobe, K Ishizawa, N Maseki, I Wasada, N Ishizuka, T Hotta, K Oshimi

Researchers from Japan led by Dr. Yamaguchi investigated a therapeutic approach for a rare malignancy that lacks an established standard approach. Nasal natural killer (NK)/T-cell lymphoma tumor expresses P-glycoprotein, conferring resistance to therapies associated with the multidrug resistance (MDR) gene.[13] As such, anthracycline-based therapies are not useful in this patient population; moreover, radiotherapy alone is associated with 2-year overall survival rates of approximately 45%. Therefore, a phase I/II trial of concurrent chemoradiotherapy was conducted in patients with newly diagnosed localized disease. Radiation doses were 50 Gy administered in 3D conformal therapy, and chemotherapy consisted of carboplatin, etoposide, ifosfamide, and dexamethasone (DeVIC). After the phase I portion of the study, reported at the 2005 American Society of Hematology annual meeting,[14] the intravenous dose of DeVIC was reduced by one third: every 3 weeks, carboplatin 200 mg/m^2 on day 1; etoposide 67 mg/m^2 on days 1–3; ifosfamide 1.0 g/ m^2 on days 1–3; and dexamethasone 40 mg on days 1–3. Twenty-seven patients were evaluated in the phase II portion (median age, 56 years; 17 male), and 26 were evaluable for response. With a median follow-up of 32 months (range, 24–62), the 2-year overall survival rate was 78% (95% confidence interval [CI], 57–89%), and 20 patients achieved CR, 1 PR, and 2 stable disease. Three patients experienced progressive disease. The CR rate and ORR were 77% and 81%, respectively. No treatment-related deaths occurred during the study. Grade 4 hyponatremia and dermatitis due to radiotherapy were observed in a single patient each. The most common nonhematologic grade 3 toxicities were mucositis due to radiotherapy and infection, both observed in 30% of patients. Concurrent radiotherapy and DeVIC, which is not impeded by expression of MDR, is considered a safe and effective treatment for localized nasal NK/T-cell lymphoma. Further investigation is warranted in this setting.

8554 A Phase II Study of Bortezomib in Combination With Intensified CHOP-like Regimen in Patients With Previously Untreated T-cell Lymphoma: Results of the GELA LNH05-1T Trial[15]

A Delmer, O Fitoussi, P Gaulard, G Laurent, D Bordessoule, F Morschhauser, C Ferme, H Tilly, C Gisselbrecht, B Coiffier; Groupe d'Étude des Lymphomes de l'Adulte

Although commonly used in the treatment of PTCL, the combination chemotherapeutic regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is associated with poor survival and alternative strategies have yet to emerge. To this end, a multicenter phase II study was initiated to assess the combination of the proteasome inhibitor bortezomib with an intensified CHOP-like regimen. Bortezomib is currently approved by the FDA for the treatment of multiple myeloma[16] and mantle-cell lymphoma.[17] In this study design, patients received induction therapy consisting of 4 bimonthly cycles of doxorubicin (75 mg/m^2 on day 1), cyclophosphamide (1,200 mg/m^2 on day 1), vindesine (2 mg/m^2 on days 1 and 5), bleomycin (10 mg on days 1 and 5), and prednisone (days 1–5; ACVBP), followed by bimonthly sequential consolidation therapy consisting of high-dose methotrexate (2 courses), etoposide and ifosfamide (4 courses), and cytarabine (2 courses). Bortezomib (1.5 mg/m^2) was administered on days 1 and 5 of each ACVBP cycle and on days 1, 8, and 15 every 4 weeks during the consolidation phase, for a total of 20 injections during the full course of treatment. A total of 57 patients (median age, 52.5 years), most with angioimmunoblastic T-cell lymphoma or PTCL-u, were enrolled. Of these patients, 46 (81%) completed induction therapy and 28 (49%) completed the consolidation phase, with the remainder experiencing disease progression. A total of 22 (39%) patients had died, mostly due to lymphoma, at the time of reporting. The amount of bortezomib administered as a percentage of the planned dose during induction was 98% and during consolidation was in the range of 90 to 95%.

The researchers observed that thrombocytopenia was more pronounced than previously observed with ACVBP alone but no life-threatening hemorrhagic event occurred. In conclusion, it was found that the combination of bortezomib with ACVBP does not lead to unexpected neurologic or platelet-related toxicities. But the response rate of the combination in patients with PTCL does not appear higher than historically observed response rates with ACVBP alone in this cohort.

8558 Autologous and Allogeneic Transplantation for Aggressive T-cell Lymphomas: A Single Institution Experience[18]

F Lansigan, D Cooper, S Seropian, F Foss

Although allogeneic and autologous stem-cell transplantation have been used for the treatment of aggressive T-cell lymphomas, as consolidation in first remission and at relapse, the role of transplantation remains to be defined. Dr. Lansigan and coworkers reported on a decade-long experience at Yale Comprehensive Cancer Center using these modalities in 42 patients with a variety of T-cell lymphomas (Table 2). The median ages for allogeneic and autologous transplantation were 51 and 52 years, with patients having received a median of 3 and 1 prior therapies, respectively. Among those receiving allogeneic transplantation, 14 patients had matched and 4 had matched-unrelated donors; 7 and 11 patients underwent ablative and reduced-intensity conditioning, respectively. The median time from diagnosis to allogeneic transplantation was 18 months, with a median of 29 months of follow-up. The 100-day transplant-related, relapse, and nonrelapse mortality for patients who received allogeneic transplantation was 11%, 11%, and 33%, respectively. The 1- and 2-year overall survival rates were 78% and 67% and 1- and 2-year PFS rates were 68% and 53%, respectively, in the allogeneic transplantation setting (*P*=.28). Six patients who received allogeneic transplantation had prior autologous transplantation and had a poorer overall survival than those who did not previously undergo autologous transplantation (32 vs 60 months), but the results did not reach statistical significance (*P*=.15). The median time from diagnosis to autologous transplantation was 8 months, with a median of 24 months of follow-up. The 100-day transplant-related, relapse, and nonrelapse mortality for patients who received autologous transplantation was 4%, 33%, and 8%, respectively. The 1- and 2-year overall survival rates were 74% and 60% and 1- and 2-year PFS rates were 52% and 45% in the autologous transplantation setting (*P*=.28). Among patients who underwent autologous transplantation, 14 (58%) were transplanted in first CR, and 10 (42%) in second CR or beyond or PR. Patients transplanted in first CR had significantly better PFS (57 vs 17 months; *P*=.007) and overall survival (76 vs 29 months; *P*=.004) than those transplanted later or in PR. One patient received allogeneic transplantation in first CR and is still alive at 33 months. Dr. Lansigan and coworkers concluded that outcomes for autologous transplantation are superior when the procedure is done in a patient's first CR. For patients with resistant or relapsed disease, allogeneic transplantation appears to be the superior modality. A prospective, randomized trial comparing autologous versus allogeneic transplantation in first CR is considered to be warranted based on these experience of Yale Comprehensive Cancer Center.

Table 2. Yale Comprehensive Cancer Center Experience (8/1997–12/2007) With Stem Cell Transplantation: Disease Types by Modality

	Allogeneic, n (N=18)	Autologous, n (N=24)
PTCL-u	4	6
Angioimmunoblastic	3	4
Panniculitis-like	2	—
CTCL with large cell transformation	2	1
Natural killer cell	2	—
Anaplastic large cell	2	12 (ALK+, n=5; ALK-, n=5; ALK unknown, n=2)
Hepatosplenic	1	—
Enteropathic	1	—
Refractory CTCL	1	—
T-lymphoblastic	—	1

In related single-institution findings from H. Lee Moffitt Cancer Center and Research Institute, Dr. Vigil and associates conducted a retrospective review of their institution's experience (1/1997–/2008) with autologous stem-cell transplantation in patients with PTCL.[19] Twenty-nine patients (median age, 51 years) were stratified according to International Prognostic Index (IPI) score, histology, and disease status at time of transplantation. Patients had anaplastic T-cell lymphoma (n=13), PTCL-u (n=18), and angioimmunoblastic T-cell lymphoma (n=6). Seventeen patients (58.62%) presented with an IPI score greater than 2. At the time of transplantation, 4 patients were in CR, 15 at first relapse, 4 in greater than one episode, and 6 had refractory disease. One-year overall survival was estimated at 72% and relapse-free survival at 62%. It was found that patients in the lower risk category demonstrated a higher likelihood of longer survival (hazard ratio=3.4), but this outcome was not statistically significant (*P*=.136). Disease status at time of transplantation was considered prognostic, and new methods for assessing minimal residual disease would be considered useful for predicting outcome.

8561 PROPEL: Results of the Pivotal, Multicenter, Phase II Study of Pralatrexate in Patients With Relapsed or Refractory Peripheral T-cell Lymphoma[20]

O O'Connor, B Pro, L Pinter-Brown, L Popplewell, N Bartlett, M Lechowicz, K Savage, B Coiffier, M Saunders, S Horwitz

Pralatrexate, a novel targeted antifolate 10-deazaaminopterin derivative, is designed to overcome limitations of methotrexate.[21] By accumulating preferentially in cancer cells through enhanced polyglutamylation, pralatrexate achieves antitumor activity. The pivotal, phase II, nonrandomized, open-label study, PROPEL, treated 111 patients with relapsed or refractory PTCL (evaluable for efficacy, n=109; PTCL-u, n=59 [53%]). Patients were heavily pretreated, having had failed a median of 3 prior regimens; 78 patients (70%) failed CHOP, and 18 (16%) previously underwent autologous stem cell transplantation. Other prior therapies included EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), bexarotene, denileukin diftitox, and photopheresis, among others. A total of 25% of patients did not achieve response to any prior therapy; 53% did not respond to last prior therapy. Pralatrexate was administered at an intravenous dose of 30 mg/m^2/week for 6 of 7 weeks, with supplementary B12 1 mg administered intramuscularly every 8–10 weeks and oral folic acid 1.0–1.25 mg/day. The primary endpoint was CR plus unconfirmed CR plus PR, according to International Workshop Criteria, with secondary endpoints of duration of response, PFS, and overall survival. Central review determined the objective response rate to be 27% (n=29), with 11 patients exhibiting CR (10%), 18 PR (17%), and 23 stable disease (21%). Although monitoring for survival remains ongoing, responses of longer than 1 year have been observed, with central review identifying the median duration of response to be 9.4 months (Figure 1). The researchers noted that 70% of responses were achieved after a single cycle, and 5 responding patients subsequently underwent stem-cell transplantation. Pralatrexate was well-tolerated, with 77 patients (69%) receiving full-dose therapy and 85% of all scheduled doses administered. The most frequent grade 3 and 4 AEs were mucositis (17% and 4%, respectively) and thrombocytopenia (14% and 19%, respectively). Other serious AEs included pyrexia, febrile neutropenia, and sepsis. A total of 8 patients died during treatment or within 1 month of the last dose of pralatrexate. The researchers concluded that pralatrexate confers substantial, durable responses in patients with relapsed or refractory PTCL regardless of prior therapy.

8564 Mature T-/NK-cell Lymphomas: Prognostic Factors and Treatment Outcome of Patients Treated on Studies of the German High-Grade Lymphoma Study Group[22]

CHOP administered in 14-day intervals (ie, CHOP-14) and cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone (CHOEP) are associated with positive outcomes compared to standard CHOP (in 21-day intervals) in patients with B-cell non-Hodgkin lymphomas. The German High-Grade Lymphoma Study Group retrospectively assessed 329 patients with

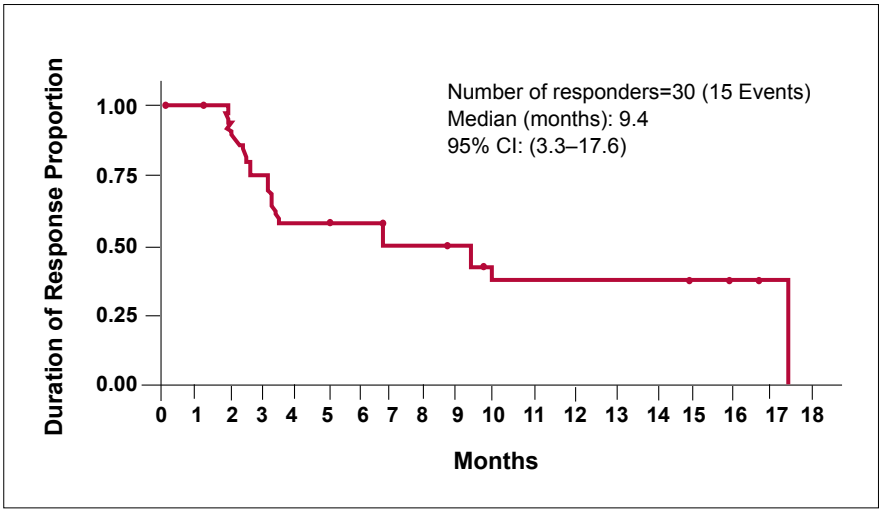

Figure 1. Kaplan-Meier estimate of duration of response per central review.

NK/T-cell lymphomas treated with CHOP-14, CHOP-21, CHOEP-14, or CHOEP-21 to identify prognostic factors and outcomes. Patients were diagnosed with ALK-positive ALCL (n=73), ALK-negative anaplastic large cell lymphoma (n=108), PTCL-u (n=68), angioimmunoblastic T-cell lymhoma (n=28), NK/T-cell lymphoma (n=18), or other rare T-cell lymphomas. Patients 60 years of age or younger received escalated doses of cyclophosphamide, doxorubicin, and etoposide. The most significant finding was that patients with ALK-positive ALCL and IPI scores of 0–2 had excellent overall (89%) and event-free survival (75%) at 3 years. Other histologies had considerably worse overall (58%) and event-free survival (44%). IPI scores of 0 or 1 were associated with favorable prognosis at 3 years: overall survival was 73% in this cohort, compared to 55%, 35%, and 19% in those with IPI scores of 2, 3, and 4 or 5, respectively. Etoposide was considered to improve time to treatment failure significantly for patients 60 years or younger (*P*=.0007). Neither CHOP-14 nor either schedule of CHOEP significantly improved outcomes for patients over 60 years of age. Younger patients (other than those with ALK-positive ALCL) and good-risk disease demonstrated a trend toward better event-free survival with the addition of etoposide to the CHOP chemotherapeutic regimen. Dose-escalated CHOP plus etoposide (megaCHOEP)[23] did not improve outcomes for young patients with poor-risk disease; as such, a prospective trial comparing MegaCHOEP to CHOEP-14 was discontinued for patients with T-cell lymphomas. In summary, the German High-Grade Lymphoma Study Group concluded that patients with ALK-positive ALCL and certain other histologies and low IPI scores achieve excellent overall survival with CHOP or CHOEP. CHOP-14 and CHOEP-14 or -21 are not associated with improved outcomes in other T-cell lymphoma settings, nor is megaCHOEP.

8572 Vorinostat in Combination With Bexarotene in Advanced Cutaneous T-cell Lymphoma: A Phase I Study[24]

R Dummer, K Hymes, W Sterry, M Steinhoff, C Assaf, H Kerl, J Ahern, S Rizvi, JL Ricker, S Whittaker

The HDAC inhibitor vorinostat is approved by the FDA for the treatment of patients who have progressive, persistent, or recurrent CTCL following 2 prior systemic treatments.[25] It has also been investigated in a phase IIb trial in heavily pretreated patients whose prior treatments included the retinoid bexarotene.[26] Dummer and associates conducted a phase I trial investigating the combination of vorinostat and bexarotene in patients with advanced CTCL, based on the hypothesis that vorinostat may enhance the latter's activity.[27] Patients at least 18 years of age with stage IB or higher progressive, persistent, or recurrent CTCL that was refractory to at least a single systemic therapy were eligible for inclusion in this trial. Vorinostat was administered in a dose-escalation fashion at a dose of 200–400 mg/day along with bexarotene 150–300 mg/m^2/day in the first part of the trial. In the subsequent part of the trial, vorinostat was administered at a fixed dose of 400 mg/day along with bexarotene in a dose-escalation fashion at 150–450 mg/day. Up to 6 cycles were repeated every 28 days. At a vorinostat dose of 300 mg/day and bexarotene dose of 150 mg/m^2/day, 3 patients experienced grade 3 hypertriglyceridemia, with 1 also experiencing grade 3 fatigue. Confirmed responses were seen in 1, 2, and 1 patient(s), respectively, in the second part of the study at vorinostat doses of 200, 400, and 400 mg/day combined with bexarotene doses of 300 mg/m^2/day, 150 mg/day, and 150 mg/day (cycle 1) then 225 mg/day (cycles 2–6). The maximum tolerated dose, the primary endpoint, in the first part of the trial was vorinostat 200 mg/day plus bexarotene 300 mg/m^2/day. The maximum tolerated dose was not reached in the second part of the study as it was discontinued early due to low enrollment. The most common drug-related AEs were hypothyroidism (35%), fatigue (30%), and hypertriglyceridemia (30%). No grade 4 or 5 drug-related AEs were reported, and 4 patients had grade 3 or lower AEs. Of 22 patients evaluable for efficacy, 4 (18%) had an objective response, and 7 (32%) experienced pruritis relief. Preliminarily, this combination is considered feasible in patients with advanced CTCL, but the dose of either drug must be reduced to avoid untoward side effects.

e19509 Effect of Dose on Denileukin Diftitox Response in Treatment-naive Cutaneous T-cell Lymphoma Subjects: A Retrospective Analysis of Three Phase III Studies[28]

NH Dang, Y Sun, J Gao

Denileukin diftitox is a recombinant fusion protein that targets the IL-2 receptor; it has been investigated in 3 phase III trials in patients with CTCL. A retrospective analysis was conducted to assess the relationship between dose level and efficacy of denileukin diftitox in treatment-naive patients with CD25-positive CTCL. Two of the

studies included patients with early or advanced CD25-positive disease as evidenced by immunostaining (>20% CD25+ cells). The other study included patients with CD25-negative disease. Subjects in the former studies received intravenous doses of 9 or 18 µg/kg/day for 5 days, repeating every 21 days for up to 8 courses; subjects in the latter study received only the higher dose. Response was confirmed by 3 observations over at least 2 consecutive courses and was reviewed by an independent committee using a weighted severity skin, blood, and lymph node count. The primary endpoint was objective response rate, with a secondary endpoint of PFS. There was broad consistency in terms of tolerability across doses and trials. Among CD25-positive patients treated at the dose of 18 µg/kg/day, vomiting (13.3% vs 34.5%) and dysgeusia (0% vs 10.9%) were more frequent. The researchers reported a trend toward higher efficacy with the higher dose level in treatment-naive patients with CD25-positive CTCL, with a statistically significant objective response rate associated with that dose.

e19511 CD3 Immunotoxin Therapy of Cutaneous T-cell Lymphoma[29]

AE Frankel, J Woo, SL Zuckero, AA Mankin, M Grable, K Mitchell, Y Lee, DM Neville

The recombinant CD3 immunotoxin A-dmDT(390)-bisFv(UCHT1) is composed of the catalytic and translocation domains of diphtheria toxin fused to 2 single-chain Fv fragments of an anti-CD30 monoclonal antibody.[30] Dr. Frankel and colleagues initiated a phase I trial in which patients with CTCL received the immunotoxin intravenously at a dose of 2.5–5 µg/kg twice daily for 4 days. Six patients received all 8 doses. Toxicities, which were mild to moderate, included fever, chills, nausea, transaminasemia, hypoalbuminemia, lymphopenia, and reactivation of Epstein-Barr virus and cytomegalovirus. These effects responded to therapy with antipyretics, antiemetics, albumin infusions, rituximab, and valganciclovir. Lymphocytopenia was observed at the end of treatment (99.9% reduction), but partial recovery followed at 2 weeks. Circulating Treg cells doubled. All patients showed anti-immunotoxin antibodies at a median of 1.3 µg/mL, which increased after 30 days to 9–1,700 µg/mL. Two of 5 evaluable patients achieved PR that lasted for 1 and more than 6 months, respectively. Dr. Frankel and colleagues concluded that this agent's clinical activity warrants application at higher doses in this setting and in other CD3-positive T-cell malignancies. Because of the associated lymphodepletion observed, it was hypothesized that this agent could be used as an immunosuppressive agent in patients with T-cell autoimmune disorders.

References

1. Bartlett N, Forero-Torres A, Rosenblatt J, et al. Complete remissions with weekly dosing of SGN-35, a novel antibody-drug conjugate (ADC) targeting CD30, in a phase I dose-escalation study in patients with relapsed or refractory Hodgkin lymphoma (HL) or systemic anaplastic large cell lymphoma (sALCL). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009; 18: Abstract 8500.
2. Oflazoglu E, Kissler KM, Sievers EL, Grewal IS, Gerber HP. Combination of the anti-CD30-auristatin-E antibody-drug conjugate (SGN-35) with chemotherapy improves antitumour activity in Hodgkin lymphoma. *Br J Haematol*. 2008;142:69-73.
3. Younes A, Forero-Torres A, Bartlett NL, et al. Multiple complete responses in a phase 1 dose-escalation study of the antibody-drug conjugate SGN-35 in patients with relapsed or refractory CD30-positive lymphomas. *Blood*. 2008;112: Abstract 1006.
4. Dueck GS, Chua N, Prasad A, et al. Activity of lenalidomide in a phase II trial for T-cell lymphoma: report on the first 24 cases. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009; 18: Abstract 8524.
5. Dimopoulos M, Spencer A, Attal M, et al; Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;357:2123-2132.
6. List A, Dewald G, Bennett J, et al; Myelodysplastic Syndrome-003 Study Investigators. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med*. 2006;355:1456-1465.
7. Demierre M, Whittaker S, Kim Y, et al. Pooled analyses of two international, multicenter clinical studies of romidepsin in 167 patients with cutaneous T-cell lymphoma (CTCL). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009; 18: Abstract 8546.
8. Kim Y, Whittaker S, Demierre MF, et al. Clinically significant responses achieved with romidepsin in treatment-refractory cutaneous T-cell lymphoma: final results from a phase 2B, international, multicenter, registration study. *Blood*. 2008;112: Abstract 263.
9. Final clinical results of a phase 2 NCI multicenter study of romidepsin in recurrent cutaneous T-cell lymphoma (molecular analyses included). *Blood*. 2008;112: Abstract 1568.
10. Piekarz RL, Frye R, Turner M, et al. Completion of the first cohort of patients with cutaneous T-cell lymphoma enrolled on a phase II trial of depsipeptide. *Blood*. 2005;106: Abstract 231.
11. Bates S, Piekarz R, Frye R, et al. Romidepsin induces clinically significant and durable responses in relapsed or refractory CTCL: a NCI international, multicenter study. Presented at the Congress of the European Hematology Association. Copenhagen, Denmark: June 12-15, 2008. Abstract 435.
12. Yamaguchi M, Tobinai K, Oguchi M, et al. Phase I/II study of concurrent chemoradiotherapy for localized nasal NK/T-cell lymphoma: final results of JCOG0211. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009; 18: Abstract 8549.
13. Harabuchi Y, Takahara M, Kishibe K, Moriai S, Nagato T, Ishii H. Nasal natural killer (NK)/T-cell lymphoma: clinical, histological, virological, and genetic features. *Int J Clin Oncol*. 2009;14:181-190.
14. Yamaguchi M, Oguchi M, Tobinai K, et al; Japan Clinical Oncology Group—Lymphoma Study Group (JCOG-LSG). Phase I/II study of concurrent chemoradiotherapy for newly-diagnosed, localized nasal NK/T-cell lymphoma: results of a phase I portion of JCOG0211-DI. *Blood*. 2005;106: Abstract 2685.
15. Delmer A, Fitoussi O, Gaulard P, et al. A phase II study of bortezomib in combination with intensified CHOP-like regimen (ACVBP) in patients with previously untreated T-cell lymphoma: results of the GELA LNH05-1T trial. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009; 18: 8554.
16. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med*. 2003;348:2609-2617.
17. O'Connor OA, Wright J, Moskowitz C, et al. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *J Clin Oncol*. 2005;23:676-684.

18. Lansigan F, Cooper D, Seropian S, Foss F. Autologous and allogeneic transplantation for aggressive T-cell lymphomas: a single institution experience. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009; 18: Abstract 8558.
19. Vigil CE, Ayala E, Sokol L. Autologous stem cell transplant in peripheral T cell lymphomas: single institution 10-year retrospective analysis. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009; 18: Abstract e19538.
20. O'Connor O, Pro B, Pinter-Brown L, et al. PROPEL: Results of the pivotal, multicenter, phase II study of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009; 18: Abstract 8561.
21. Molina JR. Pralatrexate, a dihydrofolate reductase inhibitor for the potential treatment of several malignancies. *IDrugs.* 2008;11:508-521.
22. Schmitz N, Ziepert M, Nickelsen M, et al. Mature T-/NK-cell lymphomas: prognostic factors and treatment outcome of patients treated on studies of the German High-Grade Lymphoma Study Group (DSHNHL). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009; 18: Abstract 8564.
23. Schmitz N, Kloess M, Reiser M, et al; German High-Grade Non Hodgkin's Lymphoma Study Group (DSHNHL). Four versus six courses of a dose-escalated cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen plus etoposide (megaCHOEP) and autologous stem cell transplantation: early dose intensity is crucial in treating younger patients with poor prognosis aggressive lymphoma. *Cancer.* 2006;106:136-145.
24. Dummer R, Hymes K, Sterry W. Vorinostat in combination with bexarotene in advanced cutaneous T-cell lymphoma: a phase I study. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009; 18: Abstract 8572.
25. 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.
26. 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.
27. Duvic M. Systemic monotherapy vs combination therapy for CTCL: rationale and future strategies. *Oncology (Williston Park).* 2007;21(2 suppl 1):33-40.
28. Dang NH, Sun Y, Gao J. Effect of dose on denileukin diftitox (Dd) response in treatment-naive cutaneous T-cell lymphoma (CTCL) subjects: a retrospective analysis of three phase III studies. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009; 18: Abstract e19509.
29. Frankel AE, Woo J, Zuckero SL, et al. CD3 immunotoxin therapy of cutaneous T cell lymphoma. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009; 18: Abstract e19511.
30. Frankel AE, Zuckero SL, Mankin AA, et al. Anti-CD3 recombinant diphtheria immunotoxin therapy of cutaneous T cell lymphoma. *Curr Drug Targets.* 2009;10:104-109.

Commentary

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Peripheral T-cell Lymphomas (PTCL) are a heterogeneous group of malignancies comprising a number of distinct entities. At this year's Pan Pacific Lymphoma Conference (PPLC), Dr. Elaine Jaffe from the National Cancer Institute described this group of entities as derived from either innate or adaptive immune effector cells. The adaptive immune system includes naïve, memory, and effector T-cells with both regulary and cytotoxic phenotypes, and these lymphomas occur predominantly in adults in peripheral lymph nodes rather than in extranodal sites. The nodal PTCL, angioimmunoblastic T-cell lymphomas (AILT), and adult T-cell lymphoma fall into this category. The innate immune system is involved in mucosal immunity and does not require prior antigen sensitization; the gamma delta T-cell lymphomas of the skin, liver, and intestine fall into this category, and these disorders are more predominant in children. Epstein-Barr virus (EBV) has been associated with a number of subtypes of T-cell lymphoma, particularly AILT, NK/T cell lymphomas, and T-cell lymphoproliferative disorders of childhood. EBV-associated T-cell lymphomas are more prevalent in Asia, Native America, and South America.

The International PTCL Study is a retrospective review of over 1,200 cases of aggressive T-cell lymphomas from around the world. Dr. Steven Horwitz reviewed retrospective outcomes for PTCL subgroups at the PPLC meeting. The ALK+ anaplastic large cell lymphomas had the most favorable outcomes, with failure-free survival (FFS) in excess of 5 years, while AILT, peripheral T-cell lymphoma unspecified (PTCLu), and the NK/T cell lymphomas had similar inferior outcomes, with median progression free survivals (PFS) of 6–15 months. Combination chemotherapy with CHOP type regimens has been the conventional first line approach for patients with aggressive T-cell lymphomas, albeit with modest success. Results of a retrospective review of over 3,000 patients treated with CHOP regimens was presented at American Society of Hematology (ASH) meeting last year and demonstrated an overall survival (OS) of 35%. A number of groups have investigated more intensive regimens combining novel agents. The GELA LNH05-1T trial combines CHOP with the proteosome inhibitor, bortezomib. In this trial, patients received 4 bimonthly cycles of ACVBP followed by bimonthly sequential consolidation with methotrexate, etoposide, ifosfamide, and cytarabine. Bortezomib was added on days 1 and 5 of the ACVBP cycles and on days 1, 8, and 15 of the consolidation cycles. Bortezomib was well-tolerated on this schedule with 90–96% of the planned doses delivered, and no unanticipated toxicities occurred. Of the 57 patients treated, the response rate to the combination therapy was no different than that of historical data using ACVBP alone.

In another prospective randomized trial, the German High Grade Lymphoma Study Group reported responses for 329 patients with T/NK lymphomas treated with CHOP-14, CHOP-21, or etoposide with CHOP (CHOEP-14, -21). The addition of etoposide improved the time to treatment failure for the patients under age 60 but not for the older patients. With the exception of ALK+ patients with low IPI scores (0–2) who had superior outcomes with etoposide containing regimens, the other high risk patients demonstrated no significant difference. Further, dose-escalated therapy (mega-CHOEP) did not improve outcomes for younger high-risk patients, and this arm was discontinued. These data suggest that there is no benefit to dose-intensive CHOP or to the addition of etoposide to CHOP for elderly or high-risk younger patients.

The addition of alemtuzumab or denileukin diftitox to CHOP has resulted in a higher overall response rate in phase II studies. Dr. Zinzani reviewed the data for these regimens at the PPLC meeting. A prospective trial of alemtuzumab and CHOP as first-line therapy for PTCL by Gallamini's group demonstrated a 2-year FFS of 48% and OS of 53%. In a similar study, Kim and colleagues. demonstrated a similar FFS of 43% and OS of 44%, with more favorable outcome in patients with PTCL and low IPI scores. Toxicities in both studies have included opportunistic infections and significant neutropenia. The combination of denileukin diftitox and CHOP as first-line therapy was reported by Foss and associates. The overall response rate was 86% with a 2-year PFS of 41%. There were no significant opportunistic infections reported. Another strategy has incorporated gemcitabine with CHOP (CHOP-etoposide,gemcitabine), and the event-free survival (EFS) is reported at 50% with no toxic deaths and febrile neutropenia in 15% of patients.

The NK lymphomas are often treated with combined modality therapy, including radiation in the case of localized disease, along with anthracycline-based chemotherapy. Because these tumors often overexpress p-glycoprotein, they have been resistant to most combination chemotherapy regimens. Researchers from Japan have conducted

a phase I/II trial using a non-anthracycline regimen of carboplatin, etoposide, ifosfamide, and dexamethasone (DeVIC), along with radiation therapy for localized nasal NK/T cell lymphomas. The regimen was well-tolerated with no treatment-related deaths and grade 3 mucusitis in a subset of patients. The complete response (CR) rate was high at 77% and the 2-year OS rate was 78% which compares favorably with a median 2-year survival of 50% for patients treated with anthracycline-containing regimens. In patients with advanced or refractory NK/T cell lympomas, another novel regimen containing asparaginase and methotrexate (SMILE) has demonstrated a high response rate and is currently being further investigated by the NK/T cell Study Group.

For patients with PTCL who respond to chemotherapy, consolidation with autologous or allogeneic stem cell transplantation has been implemented at many centers. Although data support the use of both approaches, there are no comparative studies and little prospective evidence to support the benefit of transplantation for individual histopathologic subgroups. In a review of autologous stem cell transplantation in PTCL presented at the Pan Pacific meeting, Dr. Horowitz presented the data from retrospective studies which show that AA-IPI of 1-0 had an OS and EFS of 53% and 50%, respectively, compared to patients with AA-IPI of 2-3, in whom the OS and EFS were 21% and 19%, respectively. In results from the GELA trials, where frontline autologous stem cell transplant was compared with chemotherapy alone, there was no difference in outcome.

Allogeneic stem cell transplantation has been used in patients with relapsed PTCL who have chemosensitive disease with reported success. It has not yet been established when allogeneic stem cell transplantation should be implemented in PTCL and in which subgroups of patients. At the American Society of Clinical Oncology (ASCO) meeting, Lansigan and colleagues reported results of 24 autologous and 18 allogeneic transplants in patients with PTCL and transformed mycosis fungoides. The median time from diagnosis to transplant was 18 months for the allo and 8 months for the auto groups, respectively. The 2-year OS and PFS in the allo group was 67% and 53%, respectively, and it was similar (60% and 45% respectively) in the auto group, with increased treatment-related mortality in the allo group balancing out the increased rate of disease recurrence in the auto group. In another study, Virgil and colleagues reported 1-year OS and PFS of 72% and 62%, respectively, for 29 patients who underwent autologous transplantation. In both studies, disease status at transplant was a strong predictor of outcome. As is the case with most transplant series in PTCL, the heterogeneity of subtypes makes it difficult to conclude which specific subtypes benefit most from this approach, and it remains to be determined which subtypes should undergo allogeneic transplantation.

A number of novel agents have been developed for patients with relapsed and refractory PTCL. Targeted therapies that have demonstrated clinical efficacy include alemtuzumab, denileukin diftitox, and antibodies targeting CD30. Results for a these promising agents were reviewed at the Pan Pacific meeting. Denileukin diftitox as a single agent in relapsed and refractory PTCL was associated with a 50% overall response rate. Agents targeting the CD30 receptor demonstrated limited activity in patients with relapsed or refractory CD30+ T-cell lymphomas and Hodgkin's disease. Bartlett and associates, reported results at ASCO of an antibody-drug conjugate consisting of anti-CD30 antibody attached to the tubulin inhibitor monomethyl auristatin E (MMAE), SGN-35. This study enrolled 17 patients in a dose escalation trial in which the MTD was not reached. Overall, 7 patients achieved CR and remain on therapy. Given that the median prior therapies was 4, these results were of significant interest, and further studies are underway to explore the activity of SGN-35 in Hodgkin's disease and CD30+ ALCL.

Two other exciting drugs with novel mechanisms of action that have demonstrated impressive clinical activity in patients with relapsed and refractory T-cell lymphomas are the HDAC inhibitor romidepsin and the antifolate pralatrexate. Both agents recently received a favorable review by the Oncologic Drugs Advisory Committee. Romidepsin has been studied in both cutaneous T-cell lymphoma and in relapsed and refractory aggressive PTCL. Demierre and associates reported pooled data from 167 patients with cutaneous T-cell lymphoma who were treated on 2 clinical trials with romidepsin. Both studies enrolled patients with relapsed or refractory CTCL and treated patients at a dose of 14 mg/m^2 weekly x 3 weeks on a 4-week cycle. The overall response rate was 41%, with a response rate of 42% in the more advanced stage (>IIB) patients. Toxicities associated with romidepsin which occur with other HDAC inhibitors, include constitutional symptoms, nausea, thrombocytopenia, and mild QTC prolongation on the electrocardiogram.

Pralatrexate is a 10-deazaaminopterin derivative which has a high affinity for the reduced folate carrier and has demonstrated a high response rate in PTCL in a phase I/II trial. O'Conner and colleagues reported results from the PROPEL trial, a phase II trial of 111 patients with relapsed or refractory PTCL treated with pralatrexate at a dose of 30 mg/m^2 weekly x 6 every 7 weeks. All patients received vitamin supplementation with vitamin B12 and folic acid. The median prior regimens for the treated patients was 3. At least 25% of patients had not responded to any of their prior therapies, and 53% had

not responded to their last prior therapy, indicating the refractoriness of the population treated on the PROPEL study. The overall response rate was 27% with 10% CR, and the median response duration was reported to be 9.4 months, although a number of patients have ongoing responses. Of note, 70% of the responses occurred after the first cycle of therapy. Adverse events associated with pralatrexate included mucusitis and thrombocytopenia. Mucusitis was well-managed during the trial by dose omissions and reductions in a minority of patients.

Results from a number of trials in cutaneous T-cell lymphoma were reviewed at both meetings. In a previously reported registration trial in heavily pretreated CTCL patients, denileukin diftitox had a 30% response rate. In a recently completed placebo-controlled trial in earlier stage patients with CTCL, a 48% overall response rate was reported. Dang and colleagues conducted a retrospective analysis of the activity of denileukin diftitox in 3 phase III trials in CTCL where patients were randomized to receive either 9 μg or 18 μg of the drug. Although adverse events including dysgeusia and vomiting were higher at the 18 μg/kg dose, there was a trend, but not a statistically significant improvement, in response rate at the higher dose. Another novel targeted agent consisting of a single chain Fv fragment of anti-CD3e fused to diphtheria toxin was tested in refractory CTCL. The fusion conjugate demonstrated clinical activity in 2 of 5 patients with a toxicity profile that included lymphopenia and viral reactivation.

A combination trial of the HDAC inhibitor vorinostat with the RXR retinoid bexarotene was explored in a phase I trial in advanced CTCL patients. The maximum tolerated dose was vorinostat 200 mg/day with bexarotene 300 mg/m^2/day, and adverse events were those attributable to both drugs, including hyperlipidemia, hypothyroidism, and fatigue. The objective response rate of 18%, however, was lower than that of either drug alone.

Lenalidomide, another agent with a novel mechanism of action, has also been explored a single-agent therapy in patients with relapsed T-cell lymphomas. Earlier studies suggested activity in patients with CTCL. Dueck and associates reported results of a phase II trial of lenalidomide at a dose of 25 mg on days 1–21 of a 28-day cycle in patients with relapsed PTCL. The ORR was 30% (7 of 23 patients, all with PR), with a median PFS of 96 days, but the median prior therapies in this group was one, suggesting that patients were less advanced than in the pralatrexate study. Toxicities included neutropenia and thrombocytopenia which was grade 4 in up to one third of the patients. Further studies with lenalidomide in relapsed T-cell lymphomas are underway.

Another novel compound with activity in T-cell lymphomas was discussed at the PPLC meeting. Aplidin is a natural product with activity in multiple myeloma and was studied in aggressive T-cell lymphomas. In a pilot study of 22 patients, 16 were efficacy evaluable; the ORR was 25%, with CR in 2 patients who progressed after transplant. One of these responses lasted for more than 24 months.

In summary, these results demonstrate a number of exciting advances in the treatment of patients with aggressive T-cell lymphomas. The role of intensification in first-line therapy has been defined for a subset of patients with good prognostic factors. The use of novel strategies and non-P-glycoprotein–related drug combinations in NK lymphomas has improved responses and has now moved to first-line approaches. Agents with novel mechanisms of action have demonstrated efficacy and durable responses in refractory patients. Combinations with these novel agents are underway and will likely yield promising results in the future.

Advances in the Treatment of T-Cell Lymphomas

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

1. In the dose-escalation trial of SGN-35, patients with what disease state achieved CR?

   a. angioimmunoblastic lymphoma
   b. systemic ALCL
   c. Hodgkin lymphoma
   d. enteropathic T-cell lymphoma

2. Lenalidomide was investigated in a phase II trial in patients with T-cell lymphoma, and an ORR of ___, with a median PFS of ___ days, was achieved.

   a. 30% and 96 days
   b. 40% and 696 days
   c. 30% and 696 days
   d. 50% and 96 days

3. In two studies of romidepsin in patients with CTCL, what was the dose administered?

   a. 16 mg/m^2 as a 4-hour infusion on days 1, 8, and 15 of a 28-day cycle
   b. 16 mg/m^2 as a 4-hour infusion on days 1, 2, and 3 of a 2 8-day cycle
   c. 14 mg/m^2 as a 4-hour infusion on days 1, 8, and 15 of a 28-day cycle
   d. 14 mg/m^2 as a 4-hour infusion on days 1, 2, and 3 of a 28-day cycle

4. What is the rationale for the use of radiation therapy combined with DeVIC in the treatment of localized nasal NK/t-cell lymphoma?

   a. Radiotherapy alone is associated with 2-year overall survival rates of approximately 45%
   b. P-glycoprotein confers resistance to anthracycline-based therapies
   c. both of the above
   d. none of the above

5. Bortezomib, investigated in a phase II study in combination with a CHOP-like regimen in patients with previously untreated T-cell lymphoma, is already approved for the treatment of what diseases?

   a. multiple myeloma
   b. mantle-cell lymphoma
   c. Burkitt lymphoma
   d. all of the above
   e. a and b

6. Which patients achieve superior benefit from allogeneic and autologous transplantation, respectively, according to results from Yale Comprehensive Cancer Center?

   a. Patients with resistant or relapsed disease and patients in first CR, respectively
   b. Patients in first CR and patients with resistant or relapsed disease, respectively
   c. Patients in first PR and patients with resistance or relapsed disease, respectively
   d. Patients with resistant or relapsed disease and patients in first PR

7. By accumulating preferentially in cancer cells through enhanced _____, pralatrexate achieves antitumor activity.

   a. apoptosis
   b. polyglutamylation
   c. demethylation
   d. transglutamination

8. In a phase I trial of a combination of vorinostat and bexarotene, what was the maximum tolerated dose in the first part of the trial?

   a. vorinostat 300 mg/day; bexarotene 200 mg/m^2/day
   b. vorinostat 300 mg/day; bexarotene 400 mg/m^2/day
   c. vorinostat 200 mg/day; bexarotene 300 mg/m^2/day
   d. vorinostat 150 mg/day; bexarotene 300 mg/m^2/day

9. The International PTCL Study found that ALK+ ALCL had the most favorable outcomes, with failure-free survival in excess of ___ years.

   a. 3
   b. 4
   c. 5
   d. 6

10. In a pilot study of aplidin conducted in 22 patients with aggressive T-cell lymphomas, the ORR was ____.

    a. 15%
    b. 25%
    c. 45%
    d. 50%

Evaluation Form 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:

- Describe the importance of new study findings in the form of selected abstracts/poster summaries in the natural history of T-cell lymphomas 1 2 3 4 5
- Cite the results of these new study findings including current clinical trials evaluating therapy in the treatment of T-cell lymphomas 1 2 3 4 5
- Explain into clinical practice the latest knowledge and methods for treating patients with T-cell lymphomas in an effort to improve current prognosis statistics 1 2 3 4 5
- Identify future research directions for all therapies in T-cell lymphomas. 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: _____

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