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Recent Advances in the Treatment of T-cell Lymphomas

A Review of Selected Presentations From the 15th Congress of the European Hematology Association and the 2010 American Society of Clinical Oncology Annual Meeting

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Target Audience: This activity has been designed to meet the educational needs of hematologists 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 patients with T-cell lymphoma. Presentations at the annual meetings of the European Hematology Association and the American Society of Clinical Oncology offered many new data on T-cell lymphoma. In addition to new data from clinical trials, there were presentations examining the epidemiology and prognosis of T-cell lymphoma, which can further stratify treatments and refine the design and interpretation of studies. This monograph reviews some of the most important new data in T-cell lymphoma and describes their relevance to the practicing physician.

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 in the natural history of T-cell lymphomas
2. Assess the results of these new study findings, including current clinical trials evaluating therapy in the treatment of T-cell lymphomas
3. Explain how to integrate into clinical practice the latest knowledge and methods for treating patients with T-cell lymphomas in an effort to improve current prognosis statistics
4. Identify future research directions for all therapies in T-cell lymphomas

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Recent Advances in the Treatment of T-cell Lymphomas

EHA#0302 A Nation-wide Survey of HTLV-1-Associated Adult T-cell Leukemia/Lymphoma in Japan[1]

Y Yamada, M Soda, M Iwanaga, Y Koga, H Hasegawa, S Kamihira, K Yamaguchi

Infection with the human T-cell leukemia virus type-1 (HTLV-1) is associated with the development of adult T-cell leukemia/lymphoma (ATLL). The prevalence of HTLV-1 varies geographically, with clustered subpopulations in Japan, South America, the Middle East, Africa, and the Caribbean carrying the infection. To assess the current epidemiology of HTLV-1 in Japan, Yamada and colleagues conducted a nationwide survey of HTLV-1 infections and outcomes, also investigating B-cell non-Hodgkin lymphoma (NHL) as an internal control. Their results were presented at the 15th Congress of the European Hematology Association (EHA).

The investigators sent questionnaires to physicians in 479 hospitals with hematology departments and received responses from 156 hospitals reporting 910 cases of ATLL and 7,164 cases of B-cell NHL diagnosed over a 2-year period beginning in January 2006. The male:female ratios for ATLL and B-cell NHL were 1.16 and 1.22, respectively.

Kyushu, an area in which HTLV-1 is endemic, accounted for 59.8% of all registered ATLL cases; the ratio of ATLL to B-cell NHL there was 1 to 4, compared with 1 to 50 in Tokyo. Nearly half of the ATLL cases (46.7%) were acute-type, 34.8% were lymphoma-type, 10.3% were smoldering-type, and 8.2% were chronic-type. The investigators noted that this distribution differed from previous reports, in which more cases were acute-type and fewer were lymphoma-type.

The mean age of individuals with HTLV-1 infection was 65.2 years, with the median age of 67 years (range, 19–94 years). Comparing these data with previous reports, the researchers noted that HTLV-1 is increasingly affecting older individuals, with the mean age increasing from 58.3 years in 1988–1989, to 60.3 years in 1994–1995, to 65.2 years in the current study. Conversely, in Jamaica and Brazil, the mean age of HTLV-1-infected individuals is much younger, at 43 years.[2,3] The researchers concluded that the older age of Japanese HTLV-1 patients should be considered when developing a therapeutic strategy, as most patients (80.8%) will be older than age 55.

Approximately 1,000 people die from ATLL in Japan each year, a mortality rate that the researchers reported has not changed in the past decade. Using the number of reported B-cell NHL cases as an internal control, the researchers calculated that the estimated annual incidence of ATLL in Japan is 1,150 cases each year.

ASCO#8051 Prognosis and Treatment of Patients With Peripheral T-cell Lymphoma: The M. D. Anderson Cancer Center Experience[4]

JV Pozadzides, G Perini, M Hess, JE Romaguera, FB Hagemeister, P McLaughlin, L Fayad, IF Khouri, C Hosing, B Pro

To gain some perspective on recent progress in the treatment of peripheral T-cell lymphoma (PTCL), Pozadzides and colleagues conducted a retrospective study evaluating treatments and outcomes in 215 patients with PTCLs (excluding cutaneous T-cell lymphoma [CTCL]) receiving care at the University of Texas M. D. Anderson Cancer Center between 1996 and 2009. Results of this study were presented at the 2010 American Society of Clinical Oncology (ASCO) Annual Meeting.

Overall, 61% of patients received intensive therapy consisting of alternating triple therapy, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine (hyper-CVAD), or a hyper-CVAD–like regimen; 37% received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, and 2% received palliative care only. Most patients (75%) did not undergo transplantation, although 19% received autologous stem cell transplant (SCT) and 6% received allogeneic SCT.

Analysis of outcomes according to treatment year in 5-year intervals showed no significant improvement from the period of 1996–2000 to the period of 2006–2009 in regard to 3-year progression-free survival (PFS; 53% vs 52%; P=.55) or 3-year overall survival (OS; 60% vs 46%; P=.08). The investigators suggested that the trend toward increased OS may reflect improvements in supportive care in addition to new treatments. However, the prognosis for these patients continues to be poor.

EHA#0303 Different Prognostic Scores in Peripheral T-cell Lymphoma (PTCL)[5]

G Gutierrez-Garcia, A García-Herrera, A Martínez, E Gainza, T Cardesa, N Villamor, L Colomo, X Setoain, S Rodríguez, E Giné, E Campo, A Urbano, A López-Guillermo

A standard prognostic score has not been established for PTCL, and thus a variety of scores have been used, including the International Prognostic Index (IPI), the Prognostic Index for PTCL (PIT), the PIT model modified by Went and colleagues,[6] and the International PTCL Project (IPTCLP) score.

To further investigate the prognostic value of the different scales, Gutierrez-Garcia and colleagues conducted a systematic comparison of these models in 120 patients with PTCL treated at a single institution from 1990–2008. Represented lymphoma subtypes included PTCL-not otherwise specific (NOS; 47%), ALK-positive anaplastic large-cell lymphoma (ALCL; 17%), angioimmunoblastic T-cell lymphoma (AITL; 16%), natural killer (NK) T-cell lymphoma (12%), hepatosplenic T-cell lymphoma (6%), and subcutaneous panniculitis–like T-cell lymphoma (2%).

The cohort included patients with stage III–IV disease (81%), extranodal involvement (76%), bone marrow infiltration (39%), high serum lactate dehydrogenase (56%), platelet count below 150×10^9/L (28%), and high □2-microglobulin levels (72% of 72 evaluable patients).

Most patients (91%) received adriamycin-containing chemotherapy; 21% received high-dose chemotherapy and SCT as first-line therapy. The median follow-up in surviving patients was 3.9 years (range, 2.8–5 years).

The investigators found that IPI was the best predictor of complete response (CR), with the CR rate ranging from 36% in low-risk disease to 14% in high-risk disease (P=.05 for low vs intermediate/high). However, in a multivariate analysis, IPTCLP was the best predictor of OS, with 5-year OS rates ranging from 58% in low-risk disease to 0% in high-risk disease (P<.0001 for low vs intermediate/high). The prognostic significance of IPTCLP was maintained among the subset of patients with PTCL-NOS.

EHA#0307 Long-term Outcome of Patients With Peripheral T-cell Lymphoma Treated With First-line Intensive Chemotherapy With Autologous Stem Cell Transplantation[7]

V Prochazka, T Papajik, E Faber, L Raida, Z Rusinakova, Z Kubova, Z Sedova, L Kucerova, M Myslivecek, K Indrak

The role of high-dose chemotherapy and autologous SCT in PTCL has not been established. Prochazka and colleagues evaluated the long-term outcome of patients treated with this strategy as first-line therapy for PTCL. A total of 29 patients received sequential chemotherapy consisting of 3 cycles of a cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide (CHOEP)-21–like regimen, 1 cycle of an ifosfamide and methotrexate-based regimen, and a priming regimen of high-dose cytosine arabinoside. Consolidation therapy consisted of myeloablative conditioning and autologous SCT. Histologic subtypes included PTCL-NOS (13 patients), ALK-negative ALCL (5 patients), ALK-positive ALCL (3 patients), ALCL with unknown ALK status (3 patients), angioimmunoblastic lymphoma (1 patient), hepatosplenic lymphoma (1 patient), Sézary syndrome (1 patient), and enteropathy-associated T-cell lymphoma (2 patients).

The median age at diagnosis was 48 years (range, 29–64 years); 77% had advanced Ann Arbor stages; 45% had an IPI score at or greater than 3; and 59% had a PIT score at or greater than 2. Twenty-six patients received sequential chemotherapy as described; 2 patients received prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue (ProMACE-CytaBOM), and 1 patient received a modified sequential chemotherapy protocol. Eighteen patients underwent high-dose chemotherapy and autologous SCT. Two patients received allogeneic SCT in first CR, and 1 patient received allogeneic SCT in the first relapse.

The overall response rate (ORR) was 76%, with 66% CR. A complete metabolic response as determined by positron emission tomography–negativity was attained in 8 of 12 evaluated patients (75%). After a median of 55 months, disease had relapsed or progressed in 48.3% of patients, and 31% of patients had died from disease progression. The median time to relapse or progression was 16.1 months.

The 2-year PFS rate was 52%, and 2-year OS rate was 65%. Eleven patients (38%) survived longer than 50 months; this long-term survival was attained in 50% of chemotherapy-sensitive patients.

ASCO#8044 Phase II Study of SMILE Chemotherapy for Newly-diagnosed Stage IV, Relapsed or Refractory Extranodal NK/T-cell Lymphoma, Nasal Type: NKTSG Study[8]

M Yamaguchi, Y Kwong, Y Maeda, C Hashimoto, W Kim, C Suh, R Hyo, S Nakamura, K Oshimi, R Suzuki

Extranodal NK/T-cell lymphoma, nasal type is a rare lymphoma subtype with no established standard treatment and low response rates to conventional chemotherapy. A new chemotherapy regimen consisting of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) previously demonstrated activity in a phase I trial.[9] In the current phase II study (also presented at the EHA meeting[10]), Yamaguchi and colleagues evaluated the efficacy and safety of the SMILE regimen in 39 patients with stage IV extranodal NK/T-cell lymphoma, nasal type, either newly diagnosed (21 patients) or with relapsed or refractory disease following first-line chemotherapy (18 patients). Patients were 16–67 years of age (median, 47 years), and 54% were male. B-symptoms were present in 56% of patients. In addition to the previously described SMILE regimen, all patients received granulocyte-colony stimulating factor (G-CSF) support starting on day 6. After the first 2 patients died from infection, eligibility criteria were revised to exclude patients with lymphocyte counts below 500 cells/mm^3, and awareness was raised regarding risk of infection. No further treatment-related deaths were reported, and the majority of patients (74%) completed the planned 2 cycles of treatment. The ORR after two 4-week cycles was 74%, including 38% CR. Grade 4 hematologic toxicities included neutropenia (92%), leukopenia (72%), thrombocytopenia (38%), and anemia (3%). Grade 3 infections developed in 41% of patients, and grade 4 infections developed in 13%. Other nonhematologic grade 3/4 toxicities occurring in at least 20% of patients included aspartate transaminase elevations (31%), hyponatremia (31%), alanine transaminase elevations (29%), and appetite loss (24%). The investigators anticipated that survival data will be available in late 2010.

ASCO#8052 Assessment of Combination Treatment With Gemcitabine, Cisplatin, and Methylprednisolone (Gem-P) in the Management of Non-Hodgkin T-cell Lymphoma[11]

K Yim, I Chau, A Horwich, C Dearden, G Morgan, A Wotherspoon, A Attygalle, B Sharma, D Cunningham

Given the poor outcomes with CHOP chemotherapy in patients with T-cell lymphoma, investigators have been evaluating alternative treatment approaches. In a clinical database analysis, Yim and colleagues identified 29 consecutive patients who received gemcitabine, cisplatin, and methylprednisolone (Gem-P) for the treatment of T-cell lymphoma. The regimen consisted of gemcitabine 1,000 mg/m^2 on days 1, 8, and 15; cisplatin 100 mg/m^2 on day 15, and methylprednisolone 1,000 mg on days 1–5 of every 4-week cycle.

The median age of enrolled patients was 53 years (range, 17–72 years), 59% were male, and disease was stage IV in 41%, stage III in 35%, and stage I/II in 24%. The most common histologic subtype represented was angioimmunoblastic lymphoma (10 patients), followed by ALCL (6 patients), PTCL-NOS (6 patients), and others.

Patients received a mean of 2.2 treatment cycles, with a range of 1–6 cycles. The ORR was 73%. CR was observed in 11 of 29 patients (38%), 10 of whom had stage III or IV disease. The ORR among patients receiving first-line therapy was slightly higher, at 80%. The investigators also noted that in 3 patients with disease relapse after at least 6 months, retreatment with the same regimen led to objective responses, including 1 CR and 2 partial responses.

In regard to safety, 55.2% of patients developed grade 3/4 thrombocytopenia, and 41.4% developed grade 3/4 neutropenia. The researchers concluded that prospective randomized trials are needed to confirm the benefit of this regimen in T-cell lymphoma.

ASCO#8046 A Phase I/II Trial of Clofarabine in Patients With Relapsed T-cell or NK-cell Lymphomas[12]

DA Mulford, BL Pohlman, PA Hamlin, F Young, E Pamer, SM Horwitz

The nucleoside analog clofarabine inhibits DNA synthesis, causing cell death. The agent is currently approved for use in pediatric patients with relapsed ALL. Preliminary studies have suggested that clofarabine is active in B-cell and T-cell malignancies, and it demonstrated CR in 2 patients with T-cell and NK-cell lymphomas. A phase I/II trial was undertaken to further assess the feasibility of clofarabine in patients with relapsed and refractory NK/T-cell lymphomas, in whom treatment options are quite limited. In the phase I portion of the study, which was designed to determine the maximum tolerated dose (MTD), clofarabine was administered starting at 4 mg/m^2 for 3 consecutive days every 3 weeks. Patients received antiviral prophylaxis and G-CSF support. After each 21-day cycle, patients received the next cycle if predefined re-treatment criteria were met, based on neutrophil and platelet counts

and resolution of nonhematologic toxicities. The cohort was expanded after determining the MTD.

A total of 30 patients were enrolled, with a median age of 60.5 years (range, 23–82 years). Patients had received a median of 3 prior therapies (range, 1–12). The MTD was 20 mg/m^2. Dose-limiting toxicities at 28 mg/m^2 included pleural effusion in 1 patient and prolonged thrombocytopenia in 1 patient. The ORR in this heavily pretreated population was 17%, including 2 CRs (including 2 of 4 patients with angioimmunoblastic T-cell lymphoma) and 3 PRs. The investigators also reported tumor reductions at lower clofarabine doses, including 8 mg/m^2 and 13.2 mg/m^2.

Grade 3/4 hematologic toxicities included leukocytes (grade 3, 43%; grade 4, 40%), thrombocytopenia (57%; 37%), neutropenia (47%; 30%), and hemoglobin (50%; 16%). Other grade 3/4 toxicities occurring in at least 10% of patients included infection (30%; 10%), hypokalemia (13%; 3%), hypercalcemia (3%; 10%), hypophosphatemia (20%; 0%), hyperglycemia (10%; 0%), and hyponatremia (13%; 0%).

ASCO#8047 Romidepsin Activity in All Three Disease Compartments (Skin, Blood, Lymph Nodes) in Patients With Cutaneous T-cell Lymphoma (CTCL)[13]

E Kim, A Rook, Y Kim, M Demierre, A Lerner, M Duvic, T Robak, J Becker, W McCulloch, S Whittaker

Romidepsin is a histone deacetylase (HDAC) inhibitor that was approved by the US Food and Drug Administration (FDA) in 2009 for the treatment of CTCL in patients who have received at least 1 prior systemic therapy. The approval was based on the results from 2 multicenter, single-arm studies of romidepsin, which showed ORRs of 35% and 34%, with 6% CR in both trials.[14,15] The median response duration was 11.1 months in one study and 14.9 months in the other.

At the ASCO 2010 meeting, Kim and colleagues provided an update from one of these studies, GPI-04-0001, reporting on the activity of romidepsin in different disease compartments using a novel composite quantitative assessment. The phase II, open-label, multicenter trial enrolled 96 patients with CTCL who had received at least 1 prior systemic therapy. Exclusion factors included concomitant use of steroids, antihistamines, QTc-prolonging agents, or CYP3A4 inhibitors, as well as cardiovascular abnormalities. Patients received romidepsin 14 mg/m^2 IV on days 1, 8, and 15 of a 28-day cycle for a planned 6 cycles.

Of the 96 patients enrolled, 61% were male and the mean age was 57 years. Disease stage was well distributed among IB (16%), IIA (14%), IIB (22%), III (24%), and IVA systemic (25%). Patients had received a median of 3 prior therapies (range, 1–8) and 2 prior skin-directed therapies. Significant blood involvement was present in 14% of patients, and 39% had lymph node involvement.

The response rate in the skin, defined as at least a 50% reduction in Severity-Weighted Assessment Tool (SWAT) or erythroderma, was 40% (8% CR). The response rate in the lymph nodes, defined as a reduction of at least 30% in the sum of the longest diameter node, was 35% (14% CR), and the response rate in the blood, defined as at least a 50% reduction in Sézary cells, was 77% (0% CR). The composite endpoint of clinical responses in all 3 compartments was 34%, with 6% CR. All patients who attained a response in all 3 compartments also had a response in the skin. However, responses in all 3 compartments were not attained by 8 of the 38 patients with skin responses (21%), 7 of the 13 patients with a blood response (54%), and 5 of the 13 patients with lymph node responses (38%). The median duration of response was 15 months.

Most drug-related toxicities were not severe; the most common grade 3 adverse events were asthenic conditions, reported in 6% of patients. Tumor lysis syndrome occurred in 2 patients. Adverse events of any grade reported in at least 20% of patients included nausea (56%), asthenic conditions (44%), vomiting (26%), and anorexia (20%).

EHA#0572 Romidepsin Experience in 317 Patients With T-cell Lymphomas[16]

BC Coiffier, S Horwitz, S Whittaker, B Pro, T Robak, A Samtsov, Y Kim, M Prince, F Foss, R Piekarz, J Nichols, S Bates

Another report on the use of romidepsin in T-cell lymphomas was presented at the 2010 Congress of the EHA. Coiffier and colleagues reviewed the safety and efficacy of single-agent romidepsin in 317 patients with T-cell lymphomas enrolled in 3 phase II, multicenter, international trials: GPI-04-0001 (96 patients with CTCL), GPI-06-0002 (103 patients with PTCL), and National Cancer Institute (NCI) 1312 (71 patients with CTCL and 47 patients with PTCL).

The mean age of enrolled patients across all 3 studies was 56–60 years (range, 21–89 years); patients had received a median of 2–4 prior therapies. Romidepsin was associated with an ORR of 34% in CTCL (6% CR) and 38% in PTCL (15% CR); median duration of response was 13.7–15 months in CTCL (range, 1–76 months) and 10 months in PTCL (range, 2–70 months).

The safety profile of romidepsin was similar in CTCL and PTCL, although rates of thrombocytopenia (any grade and grade 3/4) and grade 3/4 neutropenia were higher in PTCL, which the investigators attributed to more prior therapies and more bone marrow involvement. The most common treatment-related adverse events in CTCL were nausea (any grade, 67%; grade ≥3, 3%), fatigue (49%; 10%), and vomiting (34%; 2%). The most common treatment-related adverse events in PTCL were nausea (any grade, 53%; grade ≥3, 3%), thrombocytopenia (44%; 21%), and fatigue (43%; 7%). Discontinuation rates due to adverse events were similar in CTCL and PTCL, at 17% and 19%, respectively.

ASCO#8049 Rituximab in Combination With CHOP Regimen in Angioimmunoblastic T-cell Lymphoma: Results of the Phase II RAIL Trial—A Prospective Study of the Groupe d'Etude des Lymphomes de l'Adulte (GELA)[17]

B Joly, A Plonquet, M Grare, M Delfau-Larue, R Delarue, A Delmer, O Casasnovas, C Gisselbrecht, P Gaulard, C Haioun

The anti-CD20 monoclonal antibody rituximab is conventionally used in B-cell malignancies. However, AITL is characterized by hyperstimulation of lymphoid B cells and the presence of CD20-positive large B-blasts among the neoplastic follicular helper T-cells. The involvement of these CD20-positive cells suggests that rituximab may be beneficial in these patients. In this multicenter, phase II study, Joly and colleagues evaluated rituximab plus CHOP (R-CHOP) chemotherapy for the first-line treatment of patients with AITL. CHOP was administered in 3-week cycles, with rituximab 375 mg/m^2 given on day 1 of each cycle. Of the 25 patients treated, the median age was 67 years; 94% of patients had stage IV disease and 68% had B-symptoms. AITL histologic and phenotypic features were present in all patients, and aggregates or sheets of large CD20-positive B-blasts were detected in 6 patients. Tumor cells were detected in the peripheral blood in 7 of 15 evaluated patients, all of whom had oligoclonal or clonal T-cell populations.

Four patients stopped treatment early due to toxicities (2 patients) and disease progression (2 patients). The remaining 21 patients received 8 cycles of R-CHOP. The ORR was 80%, including 44% CRs. After a median follow-up of 24 months, the 2-year PFS rate was 42%, and the 2-year OS rate was 62%. The investigators concluded that although the regimen was well tolerated in these patients, it did not improve CR rates compared with CHOP chemotherapy.

ASCO#8053 Interim Results of Phase II Trial of Pegylated Liposomal Doxorubicin (PLD) Followed by Bexarotene in Advanced Cutaneous T-cell Lymphoma (CTCL)[18]

DJ Straus, M Duvic, SM Horwitz, KB Hymes, A Goy, FJ Hernandez-Ilizaliturri, T Feldman, B Wegner, P Myskowski

Pegylated liposomal doxorubicin (PLD) is currently approved for the treatment of Kaposi sarcoma and has been shown to concentrate in the skin. Single-agent PLD has shown activity in CTCL; early trials showed ORRs of 88% (44% CR) and 56% (20% CR), although stringent response criteria were not used in these studies.[19,20] Bexarotene is a synthetic retinoid that has also demonstrated activity in patients with relapsed/refractory CTCL, with an ORR of approximately 50%.[21,22]

An ongoing, multicenter, phase II trial is re-evaluating the activity of PLD in advanced CTCL using strict response criteria and investigating the benefit of adding sequential bexarotene after PLD. The trial has enrolled 30 of a planned 37 patients with CTCL who have adequate organ function and no acute concurrent conditions. Patients could have previously received up to 300 mg/m^2 of doxorubicin or 540 mg/m^2 of epirubicin and could be receiving topical corticosteroids, with the exception of class I agents. Erythroderma-Sézary syndrome and tumor stage T3 with intense pruritus were allowed.

Patients received PLD 20 mg/m^2 IV every 2 weeks for a total of 16 weeks, followed by 16 weeks of oral bexarotene 300 mg/m^2. The investigators assessed skin responses using the SWAT using the Composite Assessment of Index Lesion Severity.

Of the 30 patients enrolled, 15 had stage IV disease and 15 had refractory early-stage disease. After a median follow-up of 7.7 months, the ORR was 39.2%, with 7% CR. The investigators noted that these response rates were lower than had been reported in previous studies using less strict response criteria. The median PFS was 4.9 months. Treatment-related grade 3/4 adverse events were reported in 8 patients and included pain, neutropenia, and infection (6 patients) and hand-foot syndrome (2 patients). The researchers concluded that the effect of bexarotene on length of remission remains unknown.

ASCO#8050 Transcriptome Adaptation Caused by Vorinostat/Bexarotene Combination Therapy in Advanced Cutaneous T-cell Lymphoma[23]

MB Karpova, D Gunz, MJ Okoniewski, A Cozzio, K Schad, K Baumann Conzett, R Dummer

Laboratory studies are being conducted to further elucidate the molecular abnormalities associated with CTCL and to characterize molecular characteristics associated with responsiveness or lack of responsiveness to therapies. Such studies may provide insight into the development of more individualized treatment strategies for patients with CTCL.

Karpova and colleagues presented results of transcriptional analyses performed on samples from 15 patients with CTCL in a phase I study. The patients were treated with bexarotene plus the HDAC inhibitor vorinostat. Gene expression was evaluated in skin samples obtained at baseline and at day 14 of cycle 1, and expression patterns were compared between the 4 patients with a partial response, 9 patients with stable disease, and 2 patients with progressive disease.

The investigators found relatively small changes in transcriptome adaptation during therapy, with only 2- to 6-fold changes in expression. Variability between patients was the primary factor associated with molecular response. In patients with responses to therapy, pathways related to apoptosis and chemotaxis were upregulated, whereas genes associated with inflammatory responses were downregulated. Patients with responses to therapy were also more likely to have modifications in genes involved in DNA repair and fatty acid biosynthesis. Conversely, in patients with progressive disease on treatment, NOTCH and JNK stress-responsive cascades were upregulated, suggesting a NOTCH and JNK-related escape mechanism. JAK-STAT signaling was downregulated in these patients. There were no differences in expression changes between tumor and plaque lesions.

ASCO#8055 Duration of Response in Three Phase III Studies of Denileukin Diftitox in Cutaneous T-cell Lymphoma (CTCL)[24]

M Duvic, HM Prince

Denileukin diftitox (DD) is a genetically engineered fusion protein consisting of the active domain of the diphtheria toxin followed by sequences of human IL-2. DD targets malignant T-cells that express the IL-2 receptor. After binding to the IL-2 receptor, the agent is internalized; delivery of the diphtheria toxin into the cytosol causes inhibition of protein synthesis, leading to cell death.

DD has demonstrated efficacy in 3 phase III trials in patients with CD25-positive CTCL. Study 93-04-10 was a blinded, multicenter trial of 2 doses of DD in patients with recurrent or persistent disease (defined as patients who received ≥4 prior therapies for stages Ib-III disease or ≥1 prior therapy for stage IVa disease).[25] Study 93-04-11 was a double-blind, placebo-controlled, multicenter trial of DD versus placebo in less heavily pretreated patients.[26] Study 93-04-14 was an open-label rollover study of DD in selected patients from the other 2 studies and in patients excluded from protocol 93-04-11 due to low CD25 expression.

In the current analysis, Duvic and Prince evaluated the duration of response to DD across these studies. They reported a median response duration of 277 days among all DD-treated patients. This duration was approximately 3 times longer than that seen with placebo (81 days). Response rates were higher in earlier-stage disease, although among patients who attained a response, duration of response was similar across disease stage.

There was a trend toward higher response rates among patients who had received more than 1 prior therapy versus those receiving first-line therapy (40% vs 17%), and duration of response was longer in more heavily pretreated patients. Responses were also noted in the subset of patients with low CD25 expression (36 patients), who achieved an ORR of 31% and a median duration of response of 340 days.

Capillary leak syndrome (CLS) was reported in 49% of DD-treated patients and 30% of placebo-treated patients. The ORR was similar in patients who developed CLS and those who did not (36% and 40%, respectively), although the development of CLS was associated with a longer duration of response (619 vs 267 days). The most common adverse events associated with DD were nausea (56%), pyrexia (54%), fatigue (48%), rigors (47%), vomiting (29%), and diarrhea (27%).

ASCO#8045 Phase II Study of Denileukin Diftitox With CHOP Chemotherapy in Newly-diagnosed PTCL: CONCEPT Trial[27]

FM Foss, NN Sjak-Shie, A Goy, R Advani, ED Jacobsen

Clinical trials are investigating the efficacy of DD in other settings. It has been postulated that DD could be combined with chemotherapy, given its unique mechanism of action and lack of association with myelosuppression. In this multicenter phase II study, Foss and colleagues

evaluated the efficacy and safety of DD plus CHOP chemotherapy in patients with newly-diagnosed aggressive T-cell NHL according to the World Health Organization classification. A total of 49 patients received DD at 18 µg/kg/day on days 1 and 2, CHOP on day 3, and G-CSF or filgrastim on day 4, every 3 weeks for 6 cycles. Histopathologic subtypes of enrolled patients included PTCL-NOS (n=19), angioimmunoblastic T-cell lymphoma (n=10), ALCL (n=8), panniculitis-like T-cell lymphoma (n=5), intestinal T-cell lymphoma (n=3), NK/T-cell lymphoma (n=1), and hepatosplenic T-cell lymphoma (n=1). Patients with mycosis fungoides or Sézary syndrome were excluded. The median age of enrolled patients was 52 years (range, 22–80 years); B-symptoms were present in 36% of patients, and 63% had an Eastern Cooperative Oncology Group performance status of 1. Patients received a median of 6 cycles. Seven patients received only 1 cycle: 4 patients stopped treatment due to toxicity, 2 patients died from cardiac causes, and 1 patient died from rhabdomyolysis. In an intent-to-treat analysis, the ORR rate was 65%, with 51% CR. Median PFS was 12 months; 2-year estimated OS was 60%. Response rates according to histologic subtype were as follows: ALCL, 87%; angioimmunoblastic T-cell lymphoma, 80%; panniculitis-like T-cell lymphoma, 60%; PTCL-NOS, 47%; and intestinal T-cell lymphoma, 33%. The ORR among patients receiving at least 2 cycles was 86%, with CR in 73%.

The median duration of response was 29 months. The most common grade 3/4 toxicities were leukopenia (20%), thrombocytopenia (12%), and febrile neutropenia (12%). Toxicities attributed to DD included hypoalbuminemia (35%), infusion-related rigor (14%), and acute hypersensitivity (2%). The combination will be evaluated in a multicenter randomized trial of CHOP with or without DD.

ASCO#8054 Pralatrexate in Patients With Relapsed/Refractory Peripheral T-cell Lymphoma (PTCL): Relationship Between Response and Survival[28]

AR Shustov, B Pro, SM Horwitz, ED Jacobsen, A Boyd, SM Fruchtman, O O'Connor

Pralatrexate is a novel targeted antifolate agent that was approved by the FDA in 2009 for the treatment of relapsed or refractory PTCL. The approval was based on the demonstrated activity of pralatrexate in the phase II single-arm, open-label, international PROPEL (Pralatrexate in Patients With Relapsed or Refractory Peripheral T-cell Lymphoma) study.[29] The trial enrolled 111 patients with relapsed or refractory PTCL between August 2006 and April 2008. Patients received pralatrexate IV at 30 mg/m^2/week for 6 of every 7 weeks. Patients also received concurrent vitamin B_{12} 1 mg intramuscularly every 8–10 weeks and oral folic acid 1.0–1.25 mg once daily.

Of the 111 patients enrolled, 68% were male; the mean age was 57.7 years (range, 21–85 years). Patients had received a median of 3 prior therapies (range, 1–13) and 3 prior systemic therapies (range, 1–12). More than two-thirds of patients (69%) had received combination chemotherapy or SCT just prior to the study.

In the 109 patients evaluated for efficacy, pralatrexate was associated with a 29% ORR, with 10% CR by independent central review. In 63% of patients, responses occurred within the first cycle of therapy. The median duration of response was 10.1 months.

To further evaluate the effects of pralatrexate in PTCL, Shustov and colleagues analyzed the relationship between response and survival in patients receiving pralatrexate in the PROPEL study. The median OS was 14.5 months; 55% of patients survived at least 12 months.

In an independent central review, responses to pralatrexate were associated with a trend toward a reduced risk of death using a time-dependent covariate (hazard ratio [HR], 0.56; *P*=.07). The trend was less significant using a landmark analysis at cycle 1 in 90 patients (HR, 0.69; *P*=.32). Disease stabilization was also associated with an improvement in survival over progressive disease (*P*=.01), using a landmark analysis at cycle 1.

EHA#0305 Pralatrexate Activity in Patients With Relapsed/Refractory Peripheral T-cell Lymphoma: Relationship Between Response at Cycle 1 and Subsequent Survival[30]

B Coiffier, PL Zinzani, A Shustov, B Pro, S Horwitz, E Jacobsen, T Koutsoukos, S Fruchtman, O O'Connor

Coiffier and colleagues also presented results from the landmark analysis evaluating pralatrexate responses and survival at the 2010 EHA congress. In the 90 patients evaluable in the landmark analysis at cycle 1, the median survival was 17.6 months in patients with responses by cycle 1 and 13.4 months in patients without responses by cycle 1 (HR, 0.69; *P*=.32). In a per-investigator analysis of 95 patients, median survival in responders versus nonresponders was 21.3 and 8.6 months, respectively (HR, 0.46; *P*=.01). Again, these findings show that early responses to pralatrexate correlate with survival.

EHA#0300 Pralatrexate Efficacy and Tolerability in Patients With Relapsed or Refractory Cutaneous T-cell Lymphoma (CTCL)[31]

S Horwitz, M Duvic, Y Kim, J Zain, M Lechowiz, T Koutsoukos, S Fruchtman, O O'Connor

Pralatrexate is also being evaluated in other lymphoma subtypes. One consideration in developing treatments for CTCL is that the malignancy is often indolent, and thus a therapy must balance activity with toxicity to allow continuous or maintenance treatment. The current phase I dose-finding study PDX-010 was designed to identify the optimal dose of pralatrexate in CTCL, starting with 30 mg/m^2 weekly for 3 of 4 weeks and de-escalating. After completing the dose-finding phase, the investigators enrolled an additional cohort at the optimal dose.

This single-arm, open-label, multicenter study enrolled a total of 54 patients with relapsed/refractory CTCL. The median age was 62.5 years, 58% were male, and the most common CTCL subtypes included mycosis fungoides (69%) and Sézary syndrome (27%). Patients had received a median of 6.5 prior therapies (range, 1–25) and 4.0 prior systemic therapies (range, 1–11).

The optimal dose was determined to be 15 mg/m^2 weekly for 3 of 4 weeks. At this dose and schedule, the ORR in the 22 evaluable patients was 45% (all PRs). Patients continue to be treated in this study. The ORR in the 34 patients receiving higher doses was 53%, including 1 CR. Responses to pralatrexate were seen in patients with prior failure of multiple systemic therapies, including oral bexarotene (24% ORR), HDAC inhibitors (35% ORR), interferon (24% ORR), and methotrexate (40% ORR).

The only grade 3 adverse event observed at the optimal dose was mucosal inflammation, in 17% of patients. The most common grade 1/2 adverse events at the optimal dose were mucosal inflammation (22%), nausea (22%), fatigue (17%), and epistaxis (13%).

ASCO#e18568 A Phase II, Single-Arm, Open-Label Study of Pralatrexate in Patients With Aggressive Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma (NHL): Study PDX-015[32]

JE Chang, PJ Rosen, CS Magid Diefenbach, H Kacprowicz, O O'Connor

In a phase I/II study, single-agent pralatrexate induced some PRs in patients with B-cell lymphoma.[33] Moreover, combination therapy with pralatrexate and gemcitabine is demonstrating activity in an ongoing phase II, single-arm, open-label study. Chang and colleagues are evaluating the efficacy and safety of single-agent pralatrexate in patients with relapsed or refractory aggressive B-cell NHL. The study is enrolling patients with progressive or persistent disease after at least 1 prior treatment, with an ECOG performance status of 0–2 and adequate organ function.

Patients are receiving pralatrexate starting at 30 mg/m^2/week for 3 weeks of every 4-week cycle and vitamin supplementation consisting of folic acid 1 mg orally each day and vitamin B_{12} 1 mg intramuscularly every 8–10 weeks.

In this 2-stage study design, a total of 27 evaluable patients will be enrolled if a response is observed in at least 1 of the first 13 evaluable patients. The primary endpoint is objective response rate, with secondary endpoints including safety, tolerability, and pharmacokinetics.

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Commentary

Turning the Corner on T-cell Lymphomas

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When I was an oncology fellow at Stanford University Medical Center, Ron Levy, MD, the chief of medical oncology, used to tell us that you "can't trip over something if you're not moving." I have often thought how apt a phrase this is to describe much of the early attempts in treating patients with T-cell lymphomas. Several of our early successes at identifying new agents, such as pralatrexate, romidepsin, and vorinostat, have come about serendipitously as patients with T-cell lymphomas were included in broad phase I or II studies. Anecdotal responses were then followed with more robust and confirmatory experiences. Likewise, in recent years, the data generated from the large, retrospective international T-cell project have greatly contributed to our understanding and highlighted our knowledge gaps in the clinical and pathologic aspects of the T-cell lymphomas.[1-3] These efforts have helped stimulate a welcomed enthusiasm and interest in studying T-cell lymphomas. Foremost among this understanding is that our patients with aggressive T-cell lymphomas fare far worse than their counterparts with aggressive B-cell lymphoma. One overly simple hypothesis for this disparity in prognosis is that the regimens used, primarily CHOP or similar combination chemotherapy, are derived from studies of patients with large B-cell lymphoma. This has led to recent yet robust efforts to identify drugs with specific activity against aggressive T-cell lymphomas and to move away from just extrapolating treatments from the more common lymphomas. In some cases, identifying new agents has been as simple as that. This approach is so far best exemplified by the FDA approval of pralatrexate in 2009 as the first drug developed and specifically approved for relapsed or refractory PTCL. Similarly, HDAC inhibitors, such as romidepsin and vorinostat, have emerged as a class of drugs with activity for patients with the more indolent CTCLs and, in the case of romidepsin, have shown promising early activity for the more aggressive PTCL. As we can see from the preceding large number of abstracts, making progress in these uncommon diseases is both simple and not so simple.

One of the most encouraging results of this attention on T-cell lymphomas is an increasing number of abstracts focusing on many aspects of these conditions. The interest and energy devoted to this relatively uncommon group of diseases is certainly welcomed by physicians, investigators, and, perhaps most of all, patients. Novel therapies continue to be a focus at recent meetings. There were also an increased number of presentations examining the epidemiology and prognosis, which can further stratify treatments and refine the design and interpretation of studies. The preceding abstracts provide some evidence that these agents are showing clinical benefit beyond just recording response rates. One such example was a further subset analysis of the prospective PROPEL study of pralatrexate in PTCL, which showed that response correlated with survival. The PROPEL study was a multicenter study of 109 evaluable patients with relapsed or refractory T-cell lymphoma with a primary endpoint of response. Recent abstracts by Shustov and colleagues and Coiffier and associates showed a trend toward better OS in responders: the OS was 14.5 months, and among investigator-assessed responders in cycle 1, the OS was 21.3 months.[4,5] It even appears that those with a best response of only stable disease may have derived clinical benefit. It is certainly not at all surprising that responders fare better than nonresponders, and we must remember that this was an unplanned subset analysis. However, achievement of a median survival of greater than 1 year or—in some subsets—approaching 2 years, with a median fourth-line therapy in PTCL suggests that there are some patients who may be truly living longer because of the availability of these new agents.

Understanding the role, use, and potential benefit of new agents is also advanced by the very large experience reported with romidepsin by Coiffier and coworkers.[6] This abstract compiled data from 4 studies with this agent: 2 in CTCL and 2 in PTCL. As previously reported, the response rates were 34% (CR 6%) in CTCL and 38% (CR 15%) in PTCL. The median duration of responses were 13.7–15 months and 10 months in CTCL and PTCL, respectively. The reported PTCL responses, however, did not include the data from the large, multicenter trial of more than 130 patients with PTCL. This study was complete at the time of the presentation, but the central review of the responses was not yet available. It should be reported soon. If the activity from this large trial confirms the above results seen in the other PTCL study, romidepsin is likely to join the growing list of new agents that may form more active combination regimens. This abstract also highlights some of the similarities and differences in PTCL and CTCL. Although the response rates are similar at an identical dose and schedule, the hematologic toxicities varied according to underlying dis-

ease. There were significantly more grade 3/4 neutropenia and thrombocytopenia seen in PTCL patients compared to those with CTCL. This difference may be due to the intensity and number of prior cytotoxic therapies, rates of bone marrow involvement by lymphoma, or both.

To address this issue of both the potential for differing toxicities and differing expectations of toxicities and goals of therapy for patients with CTCL and PTCL, my colleagues and I performed a separate dose-finding study of pralatrexate in patients with CTCL.[7] The approved dose of pralatrexate for PTCL is 30 mg/m^2 for 6 of 7 weeks. The "optimal" dose for CTCL, determined by pre-established criteria based on efficacy and toxicity, was 15 mg/m^2 weekly for 3 of 4 weeks. With the lower dosing in the CTCL study, we found much lower rates of stomatitis and an almost complete absence of hematologic toxicity. Some of this is certainly due to the doses used. But even at the 30 mg/m^2 dose cohort, less toxicity was seen in these CTCL patients than in those with PTCL. Despite a markedly reduced dose and schedule, a high response rate of 45% was reported. This finding fulfilled the aim of this trial, as a lower dose and schedule was identified with the specific intent of sparing the CTCL patients some of the toxicity encountered by the patients with the more aggressive PTCL. It also highlights a few important issues. The doses and schedules identified for some of the new drugs in PTCL were either derived from fairly limited phase I studies or were borrowed from other diseases. Because these are rare patients, and large studies are often difficult to accomplish in a timely manner, we often have only limited data on dose. As we look to combine novel agents in combination regimens, we may need to spend more time evaluating different doses and schedules in order to optimally balance activity and toxicity.

As discussed above, several of the initial attempts to identify new agents for use in T-cell lymphomas have been successful, and it can appear that by performing a series of phase II studies, we can easily identify a new collection of active drugs. However, as more studies are done and more data reported in PTCL, we see that significant improvement will not be as simple as just focusing studies on these patients. In our clofarabine study, we sought to find a dose and schedule that would be feasible for patients with relapsed T-cell lymphoma on a 3-week cycle.[8] We found hematologic toxicity in terms of failure to recover blood counts to start the next cycle to be the primary dose-limiting toxicity, with an MTD of 20 mg/m^2 given for 3 consecutive days every 3 weeks. Unlike in some other phase II studies in T-cell lymphoma, clofarabine resulted in a response rate of only 17% in what were admittedly very heavily pretreated patients.

Even as we identify an increasing number of new agents for patients with T-cell lymphoma, we are also faced with a sobering reality: Although identifying new drugs in relapsed and refractory T-cell lymphoma is an important first step towards improving outcomes, devising new combination regimens to improve results achieved with standard upfront therapy is unlikely to be a quick or simple process. The message that CHOP is a largely inadequate therapy for the majority of patients with PTCL is an easy concept to grasp. Nonetheless, despite poor long-term results, CHOP still provides an approximately 80% response rate with a nearly 40% CR rate.[9] Devising an alternate regimen that is tolerable and surpasses an 80% response rate, let alone improves cure rates, may prove difficult and not as simple as merely identifying alternate agents and putting them together.

Several of the abstracts discussed here exemplify such attempts. Investigators at the M. D. Anderson Cancer Center presented results of various treatments in 215 patients with PTCL. Among these patients, 61% had received intensive therapy (defined as a therapy with greater dose intensity than CHOP), which consisted of hyper-CVAD–like regimens and alternating triple therapy, and 25% had received a stem cell transplant.[10] Despite the more frequent selection of aggressive therapy in recent eras, PFS from initial therapy is identical among patients treated before 2000 and those treated from 2006–2009. However, despite identical PFS, there is a trend towards improvement in OS for more recently treated patients. The authors concluded that this trend may be due to better supportive care and the increased number of new agents with activity in patients with PTCL. It would be interesting to know the rates of patients treated at relapse on a clinical trial in the different eras, and if that affected OS. Treating patients with PTCL, at least in the relapsed setting, presents an interesting irony today. Because larger studies are now being done, many of our "investigational" agents come with a greater experience and a more defined role in PTCL than commonly used but less thoroughly studied "noninvestigational agents" such as gemcitabine or denileukin diftitox.

Many novel combination regimens are being explored based on the hypothesis that adding or substituting agents with known activity in PTCL may result in better outcomes. One such combination was the gemcitabine cisplatin prednisone (Gem-P) regimen.[11] Other small phase II studies and clinical experience tell us that gemcitabine is certainly active in T-cell lymphoma. In this study, 29 patients received Gem-P instead of CHOP as initial therapy or, at relapse, after CHOP therapy. For the subset of patients treated in the first-line setting, the ORR was 80%, which is identical to that seen for CHOP in other studies.[9]

In attempts to add to CHOP, it has been similarly difficult to show clear improvement. Angioimmunoblastic

T-cell lymphoma (AITL) is known to often coexist with large Epstein Barr virus–positive B cells, and it is thought that the B cells may play a role in the genesis of this T-cell lymphoma. Anecdotal reports describe responses of AITL to rituximab.[12] The RAIL study was an attempt by GELA to capitalize on this activity and the known safety of R-CHOP.[13] But again, even though CHOP is associated with recognized suboptimal results, these results could not be surpassed just by adding additional active agents. The ORR was 80%, including 44% CR. After 2 years, PFS was 42%, a rate that the authors concluded was quite similar to that achieved with CHOP alone.

Another attempt to build upon CHOP is the CONCEPT study led by Dr. Francine Foss, in which denileukin diftitox was added to CHOP.[14] Denileukin diftitox had been shown to have single-agent activity in a previous phase II study from M. D. Anderson.[15] This study is interesting in both design and interpretation; the data suggest benefits in terms of response rate, but, somewhat unexpectedly, treatment was associated with added toxicity. Among the 49 patients who were treated, 14% were not able to get beyond cycle 1, including 3 patients who died of presumed treatment-related toxicity (2 cardiac arrests, 1 rhabdomyolysis). This level of high-grade toxicity is unexpected with CHOP or denileukin diftitox alone, and it would not have been predicted by the combination, especially because the drugs were not given on the same day (denileukin diftitox was given on days 1–2, and CHOP was given on day 3). The ORR (65%) and the median PFS were similar to or lower than the rates expected with CHOP alone. The CR rate, however, was high at 51%, suggesting that patients who completed the treatment course may have had better responses than if they had received CHOP alone. This suggestion is supported by looking at those patients who received 2 more cycles of therapy (essentially excluding the early toxicity), among whom the ORR was 86%, with a CR rate of 76%. So how to interpret these data? The most straightforward way is to look at this regimen as highly active but highly toxic—and with this data set, it is hard to conclude otherwise. But the high CR rate is intriguing, and if the investigators can isolate those patients at highest risk of early toxicity, and if those risk factors are different from the general risk factors of poor prognosis, such as high IPI or high PIT, then perhaps there is a role for this strategy in future studies. The planned randomized study is the best way to go about trying to discern whether the activity and toxicity seen in this phase II study can be separated. I would, however, emphasize that further exploration of this combination should be performed in a study, as the high early toxicity may well correlate with other predictors of poor prognosis, and it is possible that this regimen has additive or synergistic toxicity.

One novel regimen that does appear to be a clear improvement is the SMILE regimen. SMILE is a dose-intense combination of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide, and this regimen has been piloted and studied exclusively in patients with nasal NK/T-cell lymphoma. The rationale for this approach derives from the previously reported activity of a similar regimen of ifosfamide, methotrexate, etoposide and prednisone (IMEP), as well as the documented strong single-agent activity of L-asparaginase in relapsed NK/T-cell lymphoma.[16] Improvements may also be more achievable due to the reported very low response rate of nasal NK/T cell lymphoma to CHOP, which led to strategies incorporating radiotherapy as the primary or only approach for early-stage disease.[17] This regimen is quite intense, and in the initial phase I study, the maximum tolerated dose was dose level 1.[18] Nonetheless, CRs were seen in this study. In the phase II study presented at the 2010 ASCO meeting by Yamaguchi and colleagues, response data were presented for 2 cycles of SMILE in 39 patients with stage IV disease nasal NK/T-cell lymphoma (21 untreated and 18 relapsed).[19] Two infectious deaths were reported, with grade 4 hematologic toxicities present in almost all patients. The response rates were high for this disease, with an ORR of 74% and a CR rate of 30% in a disease that is generally assumed to be resistant to CHOP. I think the toxicity of this regimen suggests that it should be used with caution, and longer follow-up and rates of PFS and OS will help us understand whether this is a regimen that could be used as a standalone treatment or if it is best used prior to consolidation with radiation, high-dose therapy, or both.

We appear to be turning the corner in studying T-cell lymphomas. We have moved from treating our patients based on data from small series to larger phase II studies in the relapsed setting, and we are moving toward novel upfront regimens. However, these diseases remain a challenge, and developing and establishing better combination regimens will take an even higher level of rigor in terms of study size and design. I think the increased interest in T-cell lymphomas bodes well that progress will come, although it may be slow and will require significant effort.

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