Chemotherapeutic Advancements in Peripheral T-Cell Lymphoma

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The peripheral T-cell lymphomas (PTCLs) include a pathologic and clinically heterogeneous group of mature aggressive T-cell lymphomas, with overall inferior prognoses compared with aggressive B-cell lymphomas. Diagnosis by expert pathologic analysis is paramount in differentiating the multiple different clinicopathologic subtypes. The clinical presentations of PTCLs are variable, from that of an indolent nature to an aggressive behavior, although most have natural histories as aggressive lymphomas. First-line treatment for most PTCLs should include multi-agent chemotherapy with consideration of inclusion of etoposide chemotherapy for younger patients, as well as consolidation with autologous stem cell transplantation (SCT) in select cases. For patients with disease relapse, salvage therapy followed by autologous or allogeneic SCT should be considered. Additionally, several novel therapeutic agents have been approved by the US Food and Drug Administration (FDA) for relapsed/refractory PTCL, including romidepsin, pralatrexate, and brentuximab vedotin, the latter specifically for anaplastic large cell lymphoma. Furthermore, there are a number of new, targeted agents being studied. In order to improve outcomes for PTCL, it remains critical to consider these patients for clinical studies. In this article, we examine the recent progress and changing landscape of treatment of PTCL.
Semin Hematol 51:17–24.

The peripheral T-cell lymphomas (PTCLs) include a heterogeneous group of mature T-cell lymphomas representing approximately 10%–12% of all non-Hodgkin lymphomas (NHLs) with a high variability based on geography. The incidence is higher in the Far East in part due to its viral association.[1–3] PTCL classification, pathology, and prognostic features have been addressed elsewhere in this issue of *Seminars in Hematology*. In general, treatment of the PTCLs should be given with curative intent. The National Comprehensive Cancer Network (NCCN) guidelines advocate treatment based on prognostic indices.[4] For patients with low prognostic risk, chemotherapy alone may suffice and high-risk patients, if eligible, may benefit from consolidative autologous stem cell transplant (SCT). Here, we discuss the available and most active chemotherapy options for PTCLs. With the exception of nasal-type extranodal natural killer (NK)/T-cell lymphoma, optimal treatment approaches for individual histological subtype are lacking. For the most part, outcomes of several front-line chemotherapy combinations have been disappointing. The urge to optimize induction therapy by incorporating newer therapies such as novel agents that target dysregulated molecular pathways continues to be critically important. Most clinical trials performed prior to the 2000s grouped aggressive lymphomas together. Thus, most of the studies conducted in that era combined T- and B-cell histological subtypes into one study, making interpretation difficult. With better understanding of the molecular subtypes and varied biological behavior, more recent studies have focused on T-cell and B-cell NHLs. In this article, we review the recent progress and changing landscape of therapeutic options in PTCL.

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0037-1963/$ - see front matter

http://dx.doi.org/10.1053/j.seminhematol.2013.11.006

TREATMENT OF NEWLY DIAGNOSED PTCL

Traditionally, combination chemotherapy, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), has been recommended for the treatment of newly diagnosed PTCL. This is largely based on results extrapolated from aggressive B-cell lymphoma studies. In a 2004 retrospective study by the British Columbia Cancer Agency (BCCA) of 199 PTCL patients treated with CHOP or a CHOP-like regimen, the complete response (CR) rate was 64% and the 5-year overall survival (OS) rate was 35%.[5] Given the relatively poor outcomes with CHOP chemotherapy for patients with untreated PTCL,

there remains a continued high need for improved therapeutic strategies.

We recently reported outcomes from a large retrospective analysis of 341 newly diagnosed PTCL patients treated from 2000–2010 across nine US academic centers.[6] Interestingly, 23 (7%) patients received only palliative care and all died within 4 months of original diagnosis. Among the remaining 318 patients, the overall response rate (ORR) was 73% (61% CR) and 24% of patients had primary refractory disease. With a 38-month median follow-up, the 3-year progression-free survival (PFS) and OS rates were 32% and 52%, respectively. Older age, elevated lactate dehydrogenase (LDH), male gender, low albumin, and advanced-stage disease all predicted inferior OS on univariable analyses, while only stage remained significant on multivariable modeling. Consolidative SCT in first remission (versus not) was associated with improved survival when controlling for albumin, LDH, sex, and stage (PFS hazard ratio [HR] 0.46, $P = .02$; OS 0.43, $P = .04$) but not when adjusting for response to first-line therapy (PFS 0.55, $P = .08$; OS HR 0.47, $P = .10$).

It is also important to highlight that there are several PTCL subtypes that are uncommon and have distinctive presenting features and natural history (eg, hepatosplenic T-cell lymphoma [HSTCL], subcutaneous panniculitis-like T-cell lymphoma [SCPTCL] gamma-delta (γδ) type, extranasal NK/T-cell lymphoma, and enteropathy-associated T-cell lymphoma [EATL]); all are associated with dismal outcomes (ie, 5-year OS <5%–10%) when treated with conventional combination chemotherapy.[7] Furthermore, there are other specialized PTCL subtypes that warrant unique and specific therapeutic strategies[7a] (ie, adult T-cell leukemia leukemia/lymphoma [ATLL] subtypes, and extranodal NK/T-cell lymphoma, nasal-type, T-prolymphocytic leukemia [T-PLL], angio-immunoblastic T-cell lymphoma [AITL], discussed elsewhere in this issue of *Seminars*).

What Is the Best Induction Chemotherapy Regimen?

PTCL has consistently carried a poorer prognosis compared with B-cell lymphomas; these survival disparities are now even more evident in the post-rituximab era. Historically, it has been suggested that intensive therapeutic strategies, through either intensive induction therapy and/or consolidative high-dose therapy (HDT), may overcome the poor prognosis of PTCL.

A randomized trial, LNH93-3, was reported in 2002 for patients with newly diagnosed aggressive B- and T-cell lymphomas, evaluating the benefit of HDT with autologous SCT. Eligible patients had high-risk International Prognostic Index (IPI) scores.[8] Patients were randomized between doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP), followed by consolidation and a shortened course of only three cycles of cyclophosphamide, epirubicin, vindesine, bleomycin, and prednisone followed by consolidative autologous SCT; 84 patients with T-cell lymphoma were included. The 5-year OS was superior for the ACVBP arm compared with the SCT arm (60% *v* 46%, respectively, $P = .007$). The 5-year OS for patients who actually received the SCT was 56%. Additionally, the shortened course of induction therapy in the SCT arm likely provided inadequate induction therapy. In multivariate analysis of OS, besides bone marrow involvement, age <40 years, and treatment arm, T-cell phenotype was associated with inferior survival compared with B-cell NHLs. These results suggested in part the need for more optimal induction therapy.

In another randomized study by the GOELAMS, an alternative therapeutic schedule that included etoposide, ifosfamide, and cisplatin, alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine (VIP-reinforced ABVD) was compared with CHOP-21 in newly diagnosed PTCL.[9] The 2-year event-free survival (EFS) of the 88 randomized patients was 45% in the VIP-reinforced ABVD arm and 41% in the CHOP arm. There was no difference in ORR or CR rates between treatment arms. Furthermore, increased toxicities were noted in the experimental arm.

Similarly, the GELA conducted a randomized trial comparing ACVBP regimen to standard CHOP therapy in newly diagnosed patients with aggressive B- and T-cell lymphomas.[10] Of the 635 patients randomized, 98 had T-cell histology. In the intent-to-treat analysis, OS was statistically significant favoring the more intense ACVBP regimen. The 5-year survival rates were 46% and 38% in the ACVBP and CHOP treatment arms, respectively. Despite statistically significant higher treatment-related deaths with the more intense regimen (ie, 13% [ACBVP] *v* 7% [CHOP]), ACVBP appeared to be superior with regard to EFS and OS. However, this study was limited by the fact that the histological subtypes were a heterogeneous group, therefore tempering definite recommendations regarding upfront ACVBP in PTCL.

In a small Japanese study, higher intensity of CHOP (ie, "double CHOP") administered every 21 days with or without autologous SCT was evaluated in 11 patients.[11] This study included patients with PTCL not otherwise specified (NOS), AITL, and HSTCL. The ORR of 91% was encouraging; however, confirmation in a larger patient population is warranted.

The addition of etoposide to CHOP given at a frequency of every 2 weeks was evaluated by the NORDIC lymphoma group for patients with newly diagnosed PTCL, excluding anaplastic lymphoma kinase $(ALK)^+$ anaplastic large cell lymphoma (ALCL).[12] Patients who responded were offered autologous SCT. At a median follow-up of 2 years, 67% patients were alive. CHOP was compared with (CHOEP) Cyclophosphamide, Adriamycin, vincrisitne, etoposide and prednsione in all patients with aggressive lymphomas (B and T cell) by the German High-Grade Lymphoma Study Group. For younger patients with good prognosis, CHOEP resulted in good prognosis with a higher CR (88% *v* 79%) and EFS (69% *v* 58%). However, there was no difference in OS.[13]

In a multicenter phase II study of the cycloBEAP regimen (cyclophosphamide, vincristine, bleomycin, etoposide, doxorubicin, prednisone), 84 PTCL patients were treated.[14] CR was achieved in 92% of patients and the 5-year PFS and OS were 61% and 72%, respectively. There was no survival difference based on prognostic score. These impressive results clearly warrant further exploration in a phase III study.

Infusional chemotherapy with doxorubicin, vincristine, and etoposide followed by bolus cyclophosphamide and oral prednisone (EPOCH) was administered in 21 patients with PTCL. The ORR was 85% with 50% of patients achieving a CR. This study also included patients with disease relapse. Despite the fewer number of patients, the number of patients achieving a CR appeared to be comparable to that of patients receiving CHOP therapy.[15]

Lastly, in a retrospective analysis from the M.D. Anderson Cancer Center, 135 previously untreated PTCL patients were treated with different regimens, including (HyperCVAD) Cyclophosphamide, vincristine, adriamycin, dexamethasone or HyperCHOP. Despite high-risk disease characteristics in the intensified therapy group, there was no difference detected in survival rates. The estimated 3-year OS rates were 62% in the CHOP therapy group and 56% for patients receiving intensive therapy.[16]

SUBTYPE-SPECIFIC TREATMENT DATA/ RECOMMENDATIONS

Anaplastic Large Cell Lymphoma

Anaplastic lymphomas are characterized by the presence of large anaplastic cells, which strongly express CD30 antigen. By convention, anaplastic lymphomas can be systemic ALK^+ [carries the unique chromosomal translocation t(2;5)], systemic ALK^-, cutaneous ALCL, and ALCL associated with breast implants. ALCL can have a variable course with ALK^+ patients experiencing the best prognosis in all T-cell lymphoma subtypes. Patients with ALK^+ disease are often younger and carry the best prognosis when treated with an anthracycline-based regimen. ALK^- ALCLs also fair better than PTCL-NOS. Cutaneous ALCLs lack the ALK protein and have a favorable prognosis with a propensity to relapse.[17,18] ALCLs that occur in conjunction with breast implants are usually localized and present as fluid collections or seromas.[19,20] They have an indolent course and are ALK^-; removal of the implant may cure the disease. However, it is important to identify and differentiate patients with breast implants who present with parenchymal and systemic involvement as they tend to have an aggressive clinical course.

Adult T-Cell Leukemia Leukemia/Lymphoma

In patients with untreated aggressive ATLL (ie, acute, lymphoma, or unfavorable chronic type), a phase III Japanese study evaluated combination therapy of VCAP (vincristine, cyclophosphamide, doxorubicin, prednisone), AMP (doxorubicin, ranimustine, prednisone), and VECP (vindesine, etoposide, carboplatin, prednisone) compared with CHOP-14.[21] A total of 118 patients were enrolled, with CR rates of 40% and 25% in the VCAP-AMP-VECP arm versus the biweekly CHOP arm, respectively. Despite higher CR rates, this did not translate into improved PFS. There was no difference in OS. The 3-year OS was 24% in the VCAP-AMP-VECP arm and 13% on the CHOP arm. Toxicities were significantly higher in the experimental arm, with three toxic deaths reported. This study demonstrated superiority in attaining a CR for VCAP-AMP-VECP for newly diagnosed ATLL patients, though it did not improve PFS or OS.

It is also important to highlight the proclivity of activity of interferon-alpha (IFN-α), zidovudine, and arsenic trioxide (As_2O_3) therapy in the treatment of ATLL. Response rates of 70%–90% to combination IFN-α and zidovudine therapy have been demonstrated in both the leukemic and lymphoma subtypes, with associated median survival rates of 11–18 months.[22,23] Further, in a small phase II study of newly diagnosed chronic ATLL, treatment with As_2O_3 and IFN-α in combination with zidovudine resulted in an ORR of 100% with seven CRs.[24] Additionally, a UK study examined outcomes of 73 aggressive ATLL patients treated between 1999 and 2009 in a retrospective analysis.[24] On multivariate analysis, the use of zidovudine/IFN-α at any point in the patient's care was the only factor associated with reduction in risk of death in aggressive ATLL (HR 0.23; $P = .002$). First-line combined therapy (ie, chemotherapy with concurrent/sequential zidovudine/IFN-α) was associated with improved OS compared with chemotherapy alone. Zidovudine/IFN-α also appeared to be beneficial if given for relapse as deferred therapy; numbers were small, but of patients treated with deferred zidovudine/IFN-α, the median OS was 20 months versus 4 months if never administered ($P = .002$). Further examination of these anti-vrial agents is needed to delineate their optimal role in treating ATLL.

Subcutaneous Panniculitis-like T-Cell Lymphoma

There is increasing evidence that within the group of SCPTCLs, there is a distinction between cases with an αβ T-cell phenotype and those with a γδ phenotype.[25,26] SCPTCL αβ has been shown to have a favorable prognosis with a 5-year OS of 82%.[27] SCPTCL αβ was associated with hemophagocytic syndrome (HPS) in 17%. Furthermore, SCPTCL αβ patients without HPS had a significantly better survival than patients with HPS, with a 5-year OS of 91% versus 46% ($P < .001$). Conversely, SCPTCL γδ carries a much poorer prognosis, with a 5-year OS of 11%. This poor outcome does not appear to be affected by present of HPS or type of treatment.

In the most recent World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) classification, only SCPTCL

cases with an αβ phenotype are classified as SCPTCL. Cases previously classified as SCPTCL with a γδ phenotype, which comprised of 25% of all cases, are now classified as cutaneous γδ T-cell lymphomas.[28] Clinical course of SCPTCL is variable, ranging from indolent disease to rapidly fatal fulminant hemophagocytosis.[25,29] When warranted, treatment varies from surgery or radiotherapy to doxorubicin-based chemotherapy or high-dose chemotherapy followed by autologous SCT. Due to data supporting the excellent prognosis of SPTCL αβ without associated HPS, some investigators question the use of aggressive multi-agent chemotherapy.[27] Interestingly, a small case series has been reported where patients have achieved durable responses with the combination of corticosteroids and methotrexate.[30]

Enteropathy-Associated T-Cell Lymphoma

Following diagnosis of EATL, doxorubicin-based combination chemotherapy should be considered for each patient, and aggressive nutritional support with parenteral or enteral feeding is critical in the care of these patients.[31] Patients with known celiac disease should adhere to a gluten-free diet. The best induction regimen for EATL is not known. The European Bone Marrow Transplant group (EBMT) recently reported a retrospective analysis of autologous SCT as consolidative or salvage therapy for EATL.[32] With an approximate 4-year follow-up, PFS and OS rates were 54% and 59%, respectively, with a trend for improved survival for patients who received transplant in first remission (66% ν 36%, $P = .06$).

Hepatosplenic T-Cell Lymphoma

The clinical course of HSTCL is commonly aggressive despite multi-agent chemotherapy and median survival is often less than 1 year.[7,33] Case reports have described clinical activity with the purine analogue, pentostatin, in relapsed patients.[34–36] Alemtuzumab, both as a single agent and in combination with cladribine and fludarabine, has also been reported anecdotally to result in responses.[37–39] The Memorial Sloan-Kettering Cancer Center group reported results on 14 HSTCL patients treated with intensive chemotherapy induction followed by consolidative SCT (autologous or allogeneic).[40] At approximately 5 years of follow-up, 50% of patients were alive and disease-free. Consolidative SCT should strongly be considered in patients with newly diagnosed HSTCL.

TREATMENT OF RELAPSED/REFRACTORY DISEASE

Eligible patients should be considered for stem cell transplantation. Details of SCT are addressed separately in this issue. Here, we discuss salvage chemotherapy and combination treatments of novel therapies with traditional chemotherapy.

Chemotherapy

Zinzani et al have published results of 39 patients of whom 20 had PTCL treated with single-agent gemcitabine. All patients were treated at a dose of 1,200 mg/m^2 on days 1, 8, and 15, as a single agent. The ORR was 50% with 23% of patients attaining a CR.[41] In another study by Sallah et al, among 10 patients treated with a similar dose of gemcitabine, two achieved a CR.[42] Gemcitabine is now routinely used in patients with relapsed refractory disease. Combination therapies that include gemcitabine warrant further exploration.

The combination of gemcitabine, oxaliplatin, and dexamethasone in elderly patients was evaluated in 31 patients. The ORR was 38%, with only two patients attaining a CR. At a median follow-up of 18 months, the EFS and OS were 10 and 14 months, respectively. Despite the low response rate and duration of response, this was a well-tolerated regimen with moderate toxicities among the elderly.[43]

The chemotherapy regimen combining cisplatin, etoposide, gemcitabine, and methylprednisolone in patients with newly diagnosed or relapse PTCL was evaluated by the Southwest Oncology Group (SWOG). In this study, the ORR was 39%. Despite being a well-tolerated regimen, the response rate in this study was not promising, but this regimen offers an alternative for patients with disease relapse.[44]

Novel Therapeutic Agents in Combination With Chemotherapy

Despite the activity of autologous and allogeneic SCT in relapsed/refractory PTCL, relapses still occur. In addition, many older patients may not be amenable to intensive therapy such as SCT due to either advanced age, comorbidities, or prior toxicities. Thus, drug combinations for patients with relapsed refractory disease with increased efficacy and reduced toxicities are highly attractive. The number of agents showing activity in PTCL is promising and progress continues as the agents that are most active in PTCL are combined with chemotherapy.

In the past, limited therapeutic options were available for patients with relapsed/refractory PTCL. With improved understanding of molecular pathways, several new targeted therapeutics have garnered approval by the US Food and Drug Administration (FDA) for patients with relapsed/refractory PTCL. Further, a number of other novel treatment agents are being explored in PTCL (Table 1)[45] and are discussed by Coiffier in this issue of *Seminars*.

Denileukin diftitoxin is a fusion protein of interleukin ligand and diphtheria toxin that once bound inhibits protein synthesis of target-specific cells. Denileukin diftitoxin is FDA-approved in CTCL and it has been studied in PTCL. In a phase II study of 27 relapsed/refractory PTCL patients, the ORR was 48%. Interestingly, the

Table 1. Summary of Novel Therapeutic Agents for T-Cell Lymphoma

Mechanism/Target	Examples of Agents	Current Status
Antibody-drug conjugate	Brentuximab vedotin	FDA-approved for relapsed/refractory ALCL; ongoing studies for untreated ALCL and for relapsed/refractory non-ALCL PTCL subtypes
Anti-folate	Pralatrexate	FDA-approved for relapsed/refractory peripheral T-cell NHL
HDAC inhibitors	Romidepsin and vorinostat	Both FDA-approved for CTCL; romidepsin FDA-approved for relapsed/refractory PTCL
Proteasome inhibition	Bortezomib	Ongoing phase II studies combined with chemotherapy or novel agents for relapsed PTCL
Anti-CD25 drug conjugate	Denileukin diftitox	Modest activity as single-agent in PTCL; studies combined with CHOP for newly diagnosed T-cell NHL
IMIDs®	Thalidomide and lenalidomide	Preliminary activity in relapsed/refractory T-cell NHL
Anti-VEGF	Bevacizumab	Combined with CHOP for newly diagnosed T-cell NHL; vascular toxicities apparent
Radioimmunoconjugates	^{131}I–anti-CD45 radioantibody, ^{131}I–anti-CD25, ^{90}Y–anti-CD25, and ^{90}Y–anti-CD5	Pre-clinical and early clinical development
ALK inhibition	Diaminopyrimidines (NVP-TAE684), dialkoxyquinolines, staurosporine-like molecules	Preclinical development and early clinical development
Signaling pathways downstream of ALK	Nutlin-3a, flavopiridol, 17-allylamino-17-demethoxygeldanamycin (17-AAG) heat shock protein 90	Preclinical development and early clinical development

Abbreviations: PTCL, peripheral T-cell lymphoma; ALK, anaplastic lymphoma kinase; PTCL, peripheral T-cell lymphoma; ALCL, anaplastic cutaneous lymphoma; CTCL, cutaneous T-cell lymphoma; HDAC, histone deacetylase; CHOP, cyclophosphamide, doxorubicin, oncovin, and prednisone; IMIDs, immunomodulatory drugs; VEGF, vascular endothelial growth factor.

clinical activity was observed irrespective of CD25 status.[46] Denileukin diftitoxin has also been combined concurrently with CHOP therapy. In a single-arm phase II study, 49 patients were treated with six cycles of denileukin diftitoxin–CHOP therapy. The ORR was 65% with 55% of patients achieving CR. A phase III study has not been completed, although these phase II results appeared overall comparable to prior data with CHOP therapy alone for untreated PTCL.[47]

Bortezomib has single-agent activity in relapsed/refractory CTCL. Zinzani et al showed recently reported results with bortezomib combined with gemcitabine for relapsed/refractory PTCL.[48] Evens et al treated 16 patients with relapsed/refractory PTCL on a phase I/II study; overall efficacy appeared modest with an ORR of 32% (CR 27%).[49] However, there was unexpected toxicity, in particular hematologic, with the initial dosing schedule (ie, both agents given on days 1 and 8 every 21 days). With a modified dosing schedule (ie, days 1 and 15 every 28 days), therapy was much better tolerated and there was encouraging activity (ie, ORR and CR rates of 50%) in a small subset of patients. Bortezomib has also been evaluated together with CHOP for untreated advanced-stage PTCL patients. In a phase II study, the ORR was 76% and the median PFS was 8.8 months. Several histological subtypes were included in this trial. Interestingly, nuclear factor-κB expression did not correlate with outcome in this study, suggesting the role of other potential pathways involved in anti-apoptosis.[50] Further examination of proteasome inhibitors should be explored, including new generation agents, such as MLN9708 (ixazomib), which has been shown to have significant activity in preclinical models.[51]

Other strategies have combined novel agents with CHOP chemotherapy. In a phase II study of alemtuzumab/CHOP for untreated PTCL, 13 of 20 patients had a CR; however, the study was closed early due to a high incidence of grade 3–4 infectious complications.[52] In order to avoid

prolonged immunosuppression, CHOP was administered on a 28-day cycle in combination with alemtuzumab, the latter given on day -1.[53] The CR rate was 71% in 24 treated patients. Infectious complications were less but were still significant. Bevacizumab was combined with CHOP in a phase II Eastern Cooperative Oncology Group (ECOG) study for untreated PTCL patients. The ORR was 90%, with 49% of patients attaining CR. Despite encouraging mechanistic rationale of use of a anti-angiogenesis agent in PTLC, this study was also discontinued due to an unexpectedly higher incidence of cardiac toxicities noted in 20% of patients.[54]

The chemotherapeutic agent bendamustine has shown efficacy in relapsed/refractory PTCL. In a phase II trial for patients with relapsed/refractory PTCL, the ORR was 50%. Notably, more than 50% of patients in this study had AITL histology.[55] However, the median duration of response for patients was somewhat brief at 3.5 months. There were also significant grade 3/4 toxicities in this study, which may have been partly related to the dosing and frequency schedule. Further study of bendamustine at modified doses and in rational combinations is warranted.

CONCLUSIONS

In conclusion, despite the wide use of CHOP therapy in PTCL, with the exception of ALK^+ ALCL, outcomes in PTCL remain unsatisfactory. Intensified regimens have not appeared thus far to have proven superiority over CHOP chemotherapy. Future trials are directed toward improving response rates with the addition of novel targeted therapies with combination chemotherapy. A phase III study is comparing brentuximab and modified CHOP (without vincristine, CHP) with CHOP therapy (ECHELON-2) is ongoing and the results are eagerly awaited (NCT01777152). The challenges in conducting trials include selection of agents and the heterogenous subtypes of PTCL, which would mean an international collaborative effort. Nevertheless, continued efforts into the study of biology of PTCLs for prognostication and discovery of novel therapeutics are needed and the treatment of patients on clinical trials remains a critical mission towards improving the outcomes of these diseases.

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