Peripheral T-Cell Lymphoma: New Therapeutic Strategies

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In this article we briefly review the labeled indications for new agents for cutaneous and peripheral T-cell lymphoma, focus on data from the last 1 to 2 years, and on data from ongoing clinical trials, with the hope that in doing so we can help elucidate difficult treatment decisions.

Introduction

Peripheral T-cell lymphoma (PTCL) is a diagnostic category that encompasses a broad range of diverse but rare mature lymphomas of T-cell origin.[1] By convention, these are often divided into three clinical categories: nodal, extranodal, and leukemic. Some authorities also include a fourth category, the cutaneous variant (cutaneous T-cell lymphoma [CTCL]); others consider the staging, prognosis, and treatment of CTCL disparate enough to consider it a separate disease entity. (In practice, and for the sake of this review, we consider them separate entities.) Regardless of subtype, cases of PTCL share aggressive clinical behavior, refractoriness to conventional chemotherapy, and poor overall prognoses. An important exception, however, is anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma (ALCL), a diagnosis that can carry a favorable prognosis in many patients.[2]

Recent data suggest a significant increase in the US incidence of the most common types of PTCL.[3,4] While some of the increase may be the result of an aging population, it is also likely due to improved diagnostic techniques, particularly advances in immunohistochemistry (IHC).[2] Unfortunately, no clear improvement in outcomes has been observed on a population scale,[3] despite the fact that, since 2009, three new agents have been approved for the treatment of patients with relapsed/refractory PTCL (although it is perhaps too early to judge their effects). However, recent and planned trials continue to clarify the deployment of the new agents in this population, and trials aimed at approval for additional agents are underway. The purpose of this article is to briefly review the data from pivotal trials for those drugs approved for relapsed/refractory PTCL, focusing on recent data that inform more precise deployment of these agents, and to evaluate the early and ongoing data for novel combination and single-agent therapies.

Recently Approved Agents

A series of recent phase II, single-arm trials led to the approvals of three new drugs; what follows is a brief review of the efficacy and toxicity findings of those studies.

In 2006, the US Food and Drug Administration (FDA) approved the oral histone deacetylase (HDAC) inhibitor vorinostat (suberoylanilide hydroxamic acid) for the treatment of relapsed/refractory CTCL. The acetylation of histones is an important mechanism in the regulation of gene expression, and a large family of naturally occurring HDACs are responsible for the closure of chromatin, which results in transcriptional repression.[5] Overexpression of various HDACs has been described in various solid tumors[6,7] and hematologic malignancies (including lymphoma),[8,9] and it is thought that the excess HDAC activity leads to repression of important tumor suppressor genes, permitting oncogenic cell growth and division.[10] Vorinostat demonstrates potent and targeted inhibition of various HDAC isoforms.[11] Its approval was based on the results of a single-arm trial of 74 patients with stage IB-IVA CTCL, treated with 400 mg by mouth daily until disease progression or intolerability.[12] The overall response rate (ORR) was 30%, and the median duration of response (DOR) was over 6 months (not reached at time of reporting). Another phase II trial of 33 patients with similar disease characteristics demonstrated an ORR of 24% and a median DOR of 3.7 months.[13] The phase II PROPEL (Pralatrexate in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma) trial was the first of its kind devoted to a population of patients with relapsed/refractory PTCL; it led to the approval of the anti-folate drug pralatrexate in 2009.[14] In preclinical models,
pralatrexate demonstrated superior intracellular penetration, polyglutamylation (which extends intracellular half-life), and inhibition of tumor growth, compared with either methotrexate or pemetrexed.[15] In the PROPEL study, 115 patients with various PTCL histologic subtypes were treated at a dose of 30 mg/m², in cycles consisting of weekly treatment for 6 weeks, followed by 1 week of rest. The ORR was 29%, with an 11% complete response (CR) rate. The median progression-free survival (PFS) and overall survival (OS) were 3.5 and 14.1 months, respectively. This population had a median of three prior systemic therapies, and common toxicities consisted of mucositis, thrombocytopenia, and neutropenia. Pralatrexate was also evaluated in a dose-escalation study of 54 patients with relapsed/refractory CTCL.[16] The ORR for patients treated at between 15 and 30 mg/m² for 3 weekly doses in 4-week cycles was 61%, with a median PFS of 13 months, but the investigators judged 15 mg/m² to be the ideal dose for such patients, based on its risk/benefit ratio; this is the dose that was used for most of the patients (n = 29) included in the study. A recent report has suggested that pre-emptive leucovorin rescue can mitigate toxicity from pralatrexate while preserving efficacy,[17] but further randomized studies (now planned) and longer follow-up are needed before this can be recommended as a standard method.

Also in 2009, the HDAC inhibitor romidepsin gained approval for both PTCL and CTCL in patients whose disease had failed at least one prior systemic therapy. Similar to vorinostat, romidepsin provides potent inhibition of HDAC isoforms, although response to the drug does not seem to correlate with the degree of observed HDAC inhibition, nor with increased acetylation or restored expression of any particular gene,[10] hampering efforts to predict which patients are most likely to benefit from this agent. Two pivotal trials of romidepsin in patients with CTCL, involving a total of 167 patients, resulted in ORRs of 25% and 33%, with median DORs of 11 and 15 months, respectively.[18,19] Similar results were observed in PTCL, with one study of 47 patients showing an ORR of 38% and a median DOR of 9 months,[20] and another study of 130 patients showing a lower ORR (25%) but a longer median DOR (17 months).[21] The most common grade 3/4 toxicities were cytopenias and infections; however, remarkably high rates of nausea and fatigue/weakness (both primarily grade 1/2) were also observed.

In 2011, the FDA granted accelerated approval to the antibody-drug conjugate brentuximab vedotin, based on the results of two phase II trials, one in patients with relapsed/refractory classic Hodgkin lymphoma (cHL),[22] and another in patients with relapsed/refractory ALCL.[22] Brentuximab vedotin targets CD30, is endocytosed, and results in targeted delivery of the microtubule inhibitor monomethyl auristatin E.[23] In patients with cHL, the ORR for brentuximab vedotin was 73%, with a median DOR of 7 months; in ALCL, the ORR was 86% and the median DOR was 13 months. Notably, in both trials, the patients who achieved a CR had a substantially longer median DOR than those who achieved a partial response (PR). The most common grade 3/4 toxicities were cytopenias; peripheral neuropathy occurred in over half of patients but was mostly sensory and primarily grade 1/2. There have been four cases of progressive multifocal leuкоencephalopathy in patients receiving brentuximab vedotin,[24] leading to a boxed warning. Rare cases of serious pancreatitis have also been reported in patients receiving the drug after its FDA approval. After the approval of brentuximab vedotin for cHL and ALCL, a phase II trial evaluating its safety and efficacy in relapsed/refractory PTCL (other than ALCL), irrespective of CD30 expression, was undertaken; preliminary results were presented in June 2013.[25] Of the first 22 patients who were evaluable, 8 (36%) have demonstrated an objective response, with a seemingly higher response rate (50%) in the 10 patients with angioimmunoblastic T-cell lymphoma (AITL). Of particular note, and consistent with other early reports,[26] response to brentuximab vedotin does not seem to correlate with CD30 expression, suggesting either the presence of off-target effect(s) or limitations to current IHC techniques with respect to this antigen.

Other Early-Phase Trials

Single agents

The BELIEF trial is a phase II single-arm study of the HDAC inhibitor belinostat in patients with relapsed/refractory PTCL. The drug was given at a dose of 1,000 mg/m² IV for 5 consecutive days in 21-day cycles. Patients were treated until progression or unacceptable toxicity, and the primary endpoint was ORR. A total of 129 patients were enrolled, and the first efficacy data were reported at the American Society of Clinical Oncology Annual Meeting in June 2013.[27] The drug was well tolerated, with low rates of grade 3/4 toxicity. The ORR was 26%, including an 11% CR rate. Another HDAC inhibitor, panobinostat, has demonstrated significant activity in a phase II trial of patients with relapsed/refractory CTCL treated with a 20-mg dose on days 1, 3, and 5 of each week.[28]
bexarotene-naive patients, the ORR was 20%, compared with 15% in the 79 patients who had already received bexarotene. The median PFS was approximately 4 months for both groups. The immunomodulatory agent lenalidomide, which was approved for the treatment of multiple myeloma in 2005,[29] and for mantle-cell lymphoma in 2013,[30] was also studied in three phase II trials.[31-33] of patients with relapsed/refractory PTCL. ORRs reported in these studies ranged between 22% and 30%, with a subset analysis of one study,[33] suggesting that those patients withAITL enjoy a statistically nonsignificant trend toward improved response rates and PFS.

A phase I trial of the aurora kinase inhibitor alisertib demonstrated significant activity for this agent in the small subset of patients with relapsed/refractory PTCL.[34] This has led to further investigation of alisertib as a single agent in a Southwest Oncology Group (SWOG) trial that completed enrollment in May 2013 (ClinicalTrials.gov identifier NCT014466881; efficacy data yet to be reported), and as part of an industry-sponsored phase III trial (ClinicalTrials.gov identifier NCT01482962) in which patients are randomly assigned to treatment with either alisertib or investigator’s choice of pralatrexate, romidepsin, or gemcitabine as single agents. Enrollment in this trial began in late 2012; no data have yet been reported.

Fenretinide is a synthetic retinoic acid that has also shown striking activity in a subset of patients with PTCL. A phase I trial that included patients with multiple types of relapsed/refractory hematologic malignancies demonstrated an ORR of 36%, with documented responses lasting 3 years in those patients with PTCL.[35] A phase II trial focused on PTCL is planned, although enthusiasm for this drug is tempered by its delivery regimen (120-hr continuous infusion, every 21 days).

**Combination therapy**

Anthracycline-based combination chemotherapy appears to remain the default backbone regimen for the exploration of new agents in the treatment of younger patients (generally under age 60 years), in spite of evidence suggesting that anthracyclines do not clearly improve outcomes for such patients.[2] For example, a German cooperative group has reported their extensive experience using the combination of cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (CHOEP) in the treatment of patients with newly diagnosed PTCL.[36] In their pooled analysis of newly diagnosed PTCL patients treated with anthracycline-containing regimens as part of prospective trials, event-free survival (EFS) was significantly longer for those who received etoposide as part of initial therapy (as part of CHOEP), although the improved EFS was due in part to the subset of patients with ALK-positive ALCL, in whom the difference in outcomes reached greatest significance.

Because anthracycline-based therapy remains the default standard of care for first-line treatment of PTCL, a number of trials are underway to evaluate combinations of novel agents with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and CHOP-like therapies. For instance, a large international trial (ClinicalTrials.gov identifier NCT01420679) is currently randomizing patients with untreated PTCL who achieve a response with CHOP to either observation or pralatrexate maintenance, administered until either intolerable adverse effects or progression of disease; no safety or efficacy data have yet been reported. The combination of romidepsin plus CHOP is also being actively explored. Results of a phase Ib trial of 18 patients demonstrated that romidepsin can be safely administered at a dose of 12 mg/m² on days 1 and 8, along with conventional CHOP (forming the so-called “RoCHOP” regimen) given on day 1 of 28-day cycles. The ORR in this study was 78%, with a CR rate of 66% and a 1-year PFS of 57%, all of which approximate historical outcomes with CHOP alone.[37] Based on these data, a phase III international trial (goal accrual of 420) comparing RoCHOP with CHOP in patients with untreated PTCL, has begun enrolling patients (ClinicalTrials.gov identifier NCT01796002).

On the other hand, in an effort to obviate exposure to anthracyclines, a consortium of US investigators evaluated the regimen CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) alternating with pralatrexate in a phase II trial of 34 patients with untreated PTCL. The regimen was reasonably well tolerated, although preliminary, unpublished results seem to indicate that response rates and rates of early progression are not clearly superior to those observed with CHOP (Dr. Julie Vose, personal communication). Nonetheless, this may eventually present a viable treatment option for patients in whom anthracyclines cannot be used, and formal presentation of the data is awaited.

**Strategies Involving Stem Cell Transplantation**

A Danish group reported in late 2012 the final results of a prospective, single-arm trial evaluating autologous stem cell transplantation (SCT) as consolidation therapy for patients with newly
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A total of 160 patients, aged 18 to 67, were treated with CHOP given every 14 days; those responding after 3 cycles underwent harvesting after cycle 5 or 6, and then underwent conditioning with carmustine, etoposide, cytarabine, and either melphalan or cyclophosphamide (either BEAM or BEAC). The ORR to induction was 82%, and a total of 115 patients underwent transplantation. The 5-year PFS and OS for the entire 160-patient cohort were 44% and 51%, respectively. Only 7% of patients relapsed after 2 years, with Kaplan-Meier curves suggesting long durability of remission for a significant subset of patients. The only factors associated with improved OS on multivariate modeling were female sex and ALCL histology (favorable prognosticators), and advanced age and bone marrow involvement (adverse prognosticators). Perhaps as a result of fewer pretransplant treatment failures (26% vs 34%), the overall trial results compare favorably to the results of an earlier German trial of similar design, in which patients received CHOP-21 as induction, along with a total body irradiation–containing conditioning regimen.

An Italian multicenter, prospective trial recently reported the investigators’ experience using age-stratification, intensification of chemoimmunotherapy, and the incorporation of both autologous (auto) and allogeneic (allo) SCT into the frontline therapy for patients with PTCL. In this trial, patients aged 18 to 60 (n = 61) received CHOP plus the anti-CD52 monoclonal antibody alemtuzumab for 2 cycles, followed by 2 cycles of hyperfractionated methotrexate, cyclophosphamide, and cytarabine (HyperCHiDAM), with responding patients “biologically” randomized to either auto or allo transplantation based on the availability of a suitable sibling or matched unrelated donor. Those over age 60 (n = 25) were treated with 6 cycles of CHOP plus alemtuzumab, without planned transplant. The response rate to induction among the younger cohort was 67%; 14 patients underwent consolidative auto SCT, and 23 underwent allo SCT. Although the study was not powered to detect superiority of one transplant strategy over the other, a multivariate analysis indicated that either auto or allo SCT provided an advantage in terms of both EFS and OS at 3 years (44% and 47%, respectively), compared with those patients who did not undergo transplant (P = .0002). In those patients older than 60 years, the 4-year PFS of 27% and 4-year OS of 32% do not indicate a clear advantage to CHOP plus alemtuzumab, compared with historical outcomes for CHOP alone. Taken together, the above recent data suggest that consolidative auto SCT may be a reasonable strategy in patients with PTCL, and the results of the Danish trial suggest that CHOEP-14 may provide better long-term outcomes for those patients who can tolerate such therapy. However, without a prospective trial powered to answer the question, it is still not known whether transplant in first remission truly improves outcomes.

**Histology-Specific Treatments**

Recent single-agent and combination treatment data may permit some tailoring of therapy for PTCL patients based on histologic subtype. For instance, an intensive regimen of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) has been evaluated in Japan for patients with both previously treated and untreated extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKTL). Due to a significant number of early infectious deaths, this protocol required amendment to mitigate toxicity. Per protocol, patients achieving response to induction with 2 cycles of SMILE were treated with either additional cycles (total of 3 to 6), or were consolidated with either auto or allo SCT, at the discretion of the treating investigator. The ORR was 79%, and long-term follow-up of all 38 enrolled patients reveals encouraging 3-year OS of 59% and 75% in those patients receiving consolidative allo SCT and auto SCT, respectively; these results compare favorably with the 35% 3-year survival in those patients treated with SMILE alone. Investigators in the United States have also reported on an experience of modified SMILE, in which pegylated L-asparaginase was substituted for the 6 doses of L-asparaginase used in the original protocol, and cycle length was shortened from 4 weeks to 3 weeks, with the mandatory use of growth factors. Although only eight patients were reported on as part of this ongoing study, the tolerability appears improved, with preserved efficacy. Provocative early efficacy results using combined-modality therapy in patients with untreated ENKTL were also reported by a Chinese group.

In this single-arm trial, 38 patients (31 of whom had stage I or II disease) received CHOP plus L-asparaginase for 6 to 8 cycles, followed by radiation therapy, with fields dictated by anatomic involvement. Grade 3/4 cytopenias were observed in over 80% of patients, but 2-year PFS and OS were 80% and 94%, respectively. The investigators for the BELLIEF trial recently reported outcomes in the subset of patients with AITL treated with belinostat. Notably, the ORR was 46% (compared with 26% for the study overall),
the median DOR was 13.6 months (compared with 8.3 months for the study overall), and the median PFS was 4.2 months (compared with 1.6 months for the study overall). By comparison, those with AITL seemed to have an ORR either approximating that of the overall PTCL population when treated with romidepsin (30% vs 25%, respectively) or inferior to that of the overall PTCL population when treated with pralatrexate (8% vs 29%). However, it should be noted that the patient numbers in these situations are small; thus, such data should be interpreted with caution. Similarly, a retrospective analysis revealed that a subset of patients with AITL (n = 27) who were treated as part of the phase II registration study for romidepsin appeared to have a remarkably long DOR, with documented responses lasting over 30 months.[45] And, as noted above, lenalidomide may have slightly more activity in patients with AITL than in those with other histologic subtypes of PTCL.[33]

Adult T-cell leukemia/lymphoma (ATLL) is very aggressive and treatment-refractory, and its acute and lymphoma presentations (as opposed to chronic disease) carry the worst overall prognosis of the PTCL subtypes.[46] Chemokine receptor 4 (CCR4) expression, which occurs in high concentrations in skin-infiltrating lymphocytes,[47] portends an inferior outcome in patients with ATLL[48] and is effectively targeted by mogamulizumab (KW-0761), a defucosylated humanized anti-CCR4 monoclonal antibody that is a potent inducer of antibody-dependent cellular cytotoxicity.[49]

Mogamulizumab was granted regulatory approval in Japan in 2012 for the treatment of patients with relapsed/refractory ATLL based on a phase II trial of 26 evaluable patients with high-risk ATLL (acute, lymphoma, or unfavorable chronic type) that demonstrated a 50% ORR, with a median PFS and OS of 5.2 and 13.7 months, respectively.[50] More recently, preliminary results from a phase II trial of 29 patients with PTCL and 8 patients with CTCL demonstrated ORRs of 34% and 38%, respectively, with a PFS of 3 months for the entire cohort.[51] In addition, Japanese investigators have reported results from a randomized trial in which patients with newly diagnosed ATLL were treated with intensive multi-agent chemotherapy (VCAP-AMP-VECP [also known as LSG15], which includes treatment with vincristine, cyclophosphamide, doxorubicin, prednisone, ranimustine, vindesine, etoposide, and carboplatin), with or without mogamulizumab.[52] Although the experimental arm achieved a higher CR rate (52% vs 33%), this unfortunately did not translate into improvement in either PFS or OS. An international (Europe, North America, and South America), randomized phase III trial of single-agent mogamulizumab vs investigator’s choice in Western patients with relapsed/refractory ATLL is now accruing patients (ClinicalTrials.gov identifier NCT01626664). Anti-CCR4 therapy may also be a viable strategy for CTCL, given the proclivity for skin infiltration by lymphocytes expressing this antigen; indeed, preclinical studies support this approach.[53]

Conclusions

Current guidelines recommend anthracycline-containing regimens as the frontline treatment for healthy patients with PTCL, although the benefit of such regimens over ones without anthracyclines is based on trial populations composed almost exclusively of patients with B-cell malignancies. Response rates, PFS, and OS remain comparatively lower for patients with PTCL when treated with such regimens, and it is expected that the majority of patients with PTCL will ultimately require multiple lines of therapy, with many dying of their disease anyway. Even in patients with CTCL, in whom median survivals are much longer, relapsing disease is the rule, and most patients will die with disease, if not of it. There is thus ongoing interest in improving response rates by improving treatment combinations and improving predictors of response, and it is vital for the providers who treat these conditions to remain aware of the implications of the ever-improving therapeutic landscape.

**TABLE**

Selective Open, Actively Accruing Trials for Patients With Peripheral T-Cell Lymphoma
In spite of a rising incidence, PTCL comprises only about 10% of non-Hodgkin lymphoma, and has an incidence below 1/100,000. The population of patients with PTCL is also not ideally suited to clinical research, given the disease heterogeneity, advanced age of most patients, and frequent presence of comorbidities. A Danish population-based study of a cohort of 499 patients diagnosed with PTCL between 2000 and 2010 demonstrated that 20% of these patients were unlikely to be eligible for any clinical trial, and 40% were considered unsuitable for SCT.[54] But perhaps the most sobering revelation of this study is that of the 80% who were eligible for a clinical trial, only 11% participated in such a trial at any point during the course of their treatment. We face an exploding number of potential single-agent, combination-treatment, and transplant options for patients with both untreated and relapsed/refractory PTCL, and the best and easiest way to hasten our discovery of important advances is to promote the participation of as many providers and patients as possible in trials now or soon to be available (Table).

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