



# Novel Therapies and Role of Transplant in the Treatment of Peripheral T-Cell Lymphomas

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Peripheral T-cell lymphomas (PTCL) are an uncommon, heterogeneous group of non-Hodgkin lymphomas that carry a much poorer prognosis than their more common B-cell counterparts. The most commonly used treatment is CHOP or its variations. However, while the results with CHOP are inadequate, there is little compelling data to suggest a preferred alternate strategy. Many of these alternate strategies have been assembled from retrospective data, small case series, subset analyses, phase II studies and individual experience. The greatest experience with

alternative treatments has been with the use of high-dose therapy as consolidation. These approaches are promising, but most of the studies are retrospective and include patients with diverse prognoses, making interpretation difficult. Preliminary results of prospective trials in PTCL are only recently being reported. Perhaps more exciting have been the increasing numbers of new therapies being studied for patients with PTCL. The activities of new drugs are being described in studies specifically for PTCL, and attempts at novel combinations are beginning.

## If Not CHOP? Alternative Treatment Strategies for PTCL

CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) or its variations (so called CHOP-like therapy), although commonly used, has never been established prospectively as a preferred or even particularly effective therapy for peripheral T-cell lymphomas (PTCL). As evidenced by the preceding discussion of prognosis, the poor prognosis for most patients is primarily with CHOP. While it may seem logical to extrapolate approaches from poor-risk diffuse large B-cell lymphoma (DLBCL) to PTCL, there are minimal data to suggest this is the best approach. Even more difficult is the heterogeneity of PTCL. Because the most common subtypes of PTCL dominate most series, the conclusions drawn for these studies are most applicable to PTCL-not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL).

## Beyond CHOP—New Combinations

Many groups have evaluated intensifying chemotherapy regimens over standard-dose CHOP by either increasing doses and/or adding additional drugs.<sup>1,2</sup> Investigators at M.D. Anderson Cancer Center compared the results with CHOP to other more intensive approaches used in selected patients: Hyper-CVAD (cyclophosphamide, mesna, doxorubicin, vincristine, prednisone, methotrexate, cytarabine), Hyper-CHOP, and alternating triple therapy: ASHOP (doxorubicin, methylprednisolone, cytarabine, cisplatin), MBACOS (bleomycin, doxorubicin, cyclophosphamide, vincristine, methylprednisolone, methotrexate), and MINE (ifosfamide, mesna, mitoxantrone, etoposide).<sup>3</sup> The great

majority of patients in this retrospective review had the three most common subtypes of PTCL: PTCL-NOS, ALCL, and AITL. There was no significant difference in 3-year overall survival (OS) between patients treated with CHOP and the intensive regimens (62% versus 56%, respectively). There was a predilection for treating higher-risk patients with the more aggressive regimens and more favorable patients, including the majority with ALCL, with CHOP. When patients with ALCL were excluded from the analysis, the outcomes were inferior but again showed no improvement with the intensive approach (CHOP 3-year OS of 43% vs 49% for the more intensive therapies). The complete remission (CR) rate was also similar between the groups (CHOP 58% vs 59% for the more intensive regimens). To further this approach, the same group piloted a modification of the Hyper-CVAD regimen using HCVID DOXIL (doxorubicin HCl Liposome Injection), with pegylated doxorubicin substituted in patients with T-cell lymphomas, this time excluding those with ALK-1-positive ALCL.<sup>4</sup> Preliminary results in 38 patients showed a high overall response rate (ORR) of 87%, but a similar CR rate compared to their previous study of 59%. Progression-free survival (PFS) and OS in comparison to their historically CHOP-treated patients awaits longer follow-up.

In the International T-cell Lymphoma Clinical/Pathologic Project, there were no significant differences in the outcomes for patients who received anthracycline-containing regimens as opposed to non-anthracycline-based regimens.<sup>5</sup> The lack of anthracycline sensitivity seen in PTCL may in part be due to P-glycoprotein expression.<sup>6</sup> Thus, adding chemotherapeutics or biologics that are not susceptible to this mechanism of resistance or non-chemo-

therapeutics is attractive. Based on perceived high single agent activity in T-cell lymphomas, several groups have piloted gemcitabine-based regimens.<sup>7,8</sup> GEM-P (gemcitabine, cisplatin, methylprednisolone) showed promise in 16 mostly pre-treated patients with PTCL, of whom 11 (69%) responded.<sup>9</sup> Gemcitabine in combination with vinorelbine and filgrastim showed a superior ORR of 70% in a subset of 10 patients with PTCL compared with an ORR of 53% for a larger, heterogeneous group of patients with relapsed Hodgkin and non-Hodgkin lymphoma.<sup>10</sup> In the front-line setting, delivering an intensive regimen of CHOP-EG (cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide, gemcitabine) was feasible in 26 patients with PTCL.<sup>11</sup> At a median follow-up of 1 year, 77% of patients were alive; however, the median event-free survival was only 7 months, suggesting that durable remissions will not be seen for the majority. To formally test these strategies, the Southwestern Oncology Group is studying a novel front-line regimen: PEGS (cisplatin, etoposide, gemcitabine, solumedrol) in a Phase II study of patients with mature T-cell lymphomas.

This scenario is reminiscent of the state of DLBCL therapy prior to the inclusion of rituximab. Phase II studies suggested promising results for more intensive regimens than CHOP. However, when large controlled studies were completed, no benefit was found.<sup>12</sup> It was only when a novel drug was added, in that case rituximab, that clear improvements in outcome were seen consistently. Modeled on this approach, the monoclonal antibody alemtuzumab has recently been added to CHOP for PTCL. Alemtuzumab is a monoclonal anti-CD52 antibody that has shown activity in PTCL.<sup>13,14</sup> However, unlike rituximab, alemtuzumab is broadly immunosuppressive and is associated with Grade 3-4 infections. The GITIL (Gruppo Italiano Terapie Innovative nei Linfomi), in a prospective multicenter trial, combined alemtuzumab with CHOP for newly diagnosed PTCL.<sup>15</sup> Patients were not required to be CD52 positive. Twenty-four consecutive patients were enrolled. Histology was confirmed in 19 patients: PTCL-NOS, -8, AITL-7, ALK-negative ALCL-3, and enteropathy-associated T-cell lymphoma-1 [EATCL-1]). Only 9 of the 24 patients had 3 or 4 risk factors by the International Prognostic Index (IPI) for DLBCL. After preliminary safety was demonstrated in the first 4 patients, the next 20 patients received 8 cycles of CHOP with alemtuzumab at 30 mg intravenously on day -1 of each course. CRs were seen in 17 of 24 (71%) patients. At a median follow-up of 16 months, 13 of the 24 patients (54%) were disease-free with an estimated 2-year OS and failure-free survival of 53% and 48%, respectively. Two of the 4 CD52-negative patients progressed on treatment. Immunosuppression is a concern with alemtuzumab added to cytotoxic chemotherapy. Major infections included J-C virus reactivation, aspergillosis, staphylococcal sepsis and pneumonia as well as cytomegalovirus reactivation. The

CR rate is impressive in this trial, but the long-term OS and FFS rates, in a relatively favorable group of PTCL patients, do not appear better than in historical patients treated with CHOP. Another study combining CHOP with alemtuzumab was stopped early, despite an ORR of 80%, due to significant infectious and hematologic toxicities, including 2 treatment-related deaths.<sup>16</sup> Alemtuzumab is also being added to dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) in an ongoing trial at the National Cancer Institute (NCI) for CD52-positive PTCL.<sup>17</sup> Early results suggest a high response rate in this study including some of the poorest prognosis subtypes such as adult T-cell leukemia/lymphoma (ATLL) and hepatosplenic T-cell. As in the previous reports, unusual or opportunistic infections such as aspergillus, mucor, and BK virus reveal the degree of immunosuppression that accompanies this active regimen. Further, grade 4 neutropenia was observed in all patients, and bone marrow aplasia was observed at higher dose levels of alemtuzumab.<sup>17</sup>

In addition to balancing safety and toxicity, CD52 expression in PTCL is heterogeneous and may present a problem when incorporating alemtuzumab. In contrast to B-cell lymphomas, where near uniform CD52 expression is observed, only 35% to 40% of cases of PTCL-NOS and AITL are CD52 positive, and one small study suggested all cases of ALCL were negative.<sup>18,19</sup> As noted above, in the GITIL trial 2 of the 4 CD52-negative patients progressed on treatment. Others have also found heterogeneous expression of CD52 on T-cell lymphomas, including some reports of the majority being CD52 negative.<sup>19</sup> Some of this variability may be due the method used to detect CD52 expression, as lower-density expression is not detected by immunohistochemistry. Flow cytometry may more reliably detect CD52 expression. These issues of target expression and toxicity need to be examined further as large prospective trials are underway in Europe combining alemtuzumab with conventional and high-dose chemotherapy programs.

Other available biologic therapies being used in combination approaches for PTCL include denileukin diftitox and bevacizumab. Because these drugs do not result in additional myelosuppression they have been relatively easily combined with CHOP. The diphtheria-interleukin-2 fusion protein, denileukin diftitox, commonly used for cutaneous T-cell lymphoma (CTCL), showed a 48% response rate as a single agent in a Phase II trial for patients with relapsed PTCL.<sup>20</sup> A preliminary report of an ongoing Phase II study of CHOP with denileukin diftitox for untreated PTCL showed clinical activity; the ORR was 90%, and there was little added toxicity over CHOP.<sup>21</sup> Bevacizumab has shown anecdotal activity in PTCL, particularly AITL, and is being added to CHOP in an ongoing Eastern Cooperative Oncology Group (ECOG) trial for newly diagnosed patients with PTCL.<sup>22,23</sup>

### High-Dose Therapy and Stem Cell Transplantation

Extrapolating from poor-risk or relapsed DLBCL, the greatest published experience of an alternative primary treatment to CHOP for PTCL has been high-dose therapy and autologous stem cell transplantation (HDT-ASCT) as consolidation (**Table 1**). Several retrospective studies suggested promise for this approach, with the Spanish GEL-TAMO experience showing remarkably good results among patients in first remission.<sup>24</sup> Their review consisted of 115 patients treated at multiple centers over 10 years; OS and disease-free survival (DFS) at 5 years were 56% and 60%, respectively. The majority of their patients had PTCL-NOS (62.6%), while most of the rest had ALCL (22%). Thirty-seven (32%) had HDT-ASCT in first complete remission (CR1). Among those undergoing HDT-ASCT in CR1, the 5-year OS and DFS were 80% and 79%, respectively, with no relapses reported beyond 2 years. Except for a median age of 31, the CR1 group was not otherwise favorable, with 73% having an age-adjusted International Prognostic Index (AA-IPI) of 2-3. The number of ALCL patients undergoing transplantation in CR1 as well as ALK-1 status was not reported, though ALCL was not a favorable prognostic factor for this series as a whole. While the results for patients in CR1 are impressive, one must at least consider the role of selection bias as only 37 patients are reported from a national database spanning 10 years. An expansion of this review again stressed the importance of CR as predictive of favorable outcome, with 68% alive and 63% disease free at 5 years. When ALCL patients were excluded, the 5-year PFS declined to 55%.<sup>25</sup>

The potential benefits of consolidation with HDT-ASCT for patients in CR1 are further substantiated through several series. In a British and Australian registry series, 82 patients were described, 64 of whom underwent HDT-ASCT with approximately half in CR1.<sup>26</sup> In the CR1 group, the OS and PFS were better than expected at 62% and 59%, respectively, at 2 years; ALCL patients (ALK-1 status was unknown in the majority) fared better than those with PTCL. A registry series from Finland demonstrated similarly promising results for those in CR1 or PR1.<sup>27</sup> For those patients, 5-year OS was 63% and 5-year PFS was 64% compared to 28% for those undergoing HDT beyond first remission. Interpretation of this series is hampered by the inclusion of ALCL. Only 1 of 11 patients with systemic ALCL relapsed (all 3 of those with cutaneous ALCL relapsed) with ALCL patients fairsignificantly better than those with PTCL-NOS. However, good results are not universal for PTCL patients undergoing ASCT-HDT in CR1, with some series describing more frequent late relapses.<sup>28,29</sup>

Some of the impact of selection bias in reporting only transplanted patients may be addressed by the few prospective studies exploring the role of ASCT as consolidation. The GELA group performed a subset analysis of patients with PTCL included on the LNH93-3 study. From

March 1993 to September 1995, 370 consecutive patients with poor-risk aggressive lymphoma, defined as AA-IPI 2-3, and age 60 years or younger were randomized to receive ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) for 4 cycles or a shortened intensive induction: 1 cycle of CEOP (cyclophosphamide, epirubicin, vincristine, and prednisone) followed by 2 cycles of ECVBP (epirubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) followed by BEAM (1,3-bis(2-chloroethyl)-1-nitrosourea, etoposide, and melphalan) and ASCT.<sup>30</sup> Seventy-six patients with T-cell phenotype were included, although their specific histology was not specified. The inclusion of 76 patients with T-cell lymphoma in a study of 370 consecutive poor-risk patients sheds some light on the selection that may exist in registry studies where a much lower proportion of transplanted patients had a T-cell phenotype. Not surprisingly, T-cell phenotype emerged as a poor prognostic factor for overall survival. Among those with T-cell lymphoma treated with ACVBP 5-year EFS and OS were 30% and 39%, respectively, compared with 20% and 29%, respectively, for those undergoing the shortened induction followed by HDT-ASCT. When these data were combined with the similar LHN-87 trial and only patients achieving a CR were evaluated in a matched pair analysis, there was still no apparent benefit to consolidation with HDT-ASCT.<sup>31</sup> Non-anaplastic PTCL patients had a 5-year OS of 44% for chemotherapy only versus 49% ( $P = .87$ ) for those consolidated with HDT-ASCT. DFS results were similar: 38% versus 45% ( $P = .89$ ), respectively.

Highlighting the high rate of induction failures for PTCL, a prospective Spanish study enrolled 41 patients with PTCL planning to undergo HDT-ASCT after an alternating induction of high-dose CHOP and ESHAP (etoposide, solumedrol, cytarabine, cisplatin).<sup>32</sup> Forty-nine percent of patients had PTCL-NOS, and 29% had AITL. Forty-six percent were high-intermediate (H-I) or high risk by the IPI, with similar risk according to the PIT (prognostic index PTCL-U).<sup>33</sup> Seventeen of 41 patients (41%) progressed prior to transplantation, and the 4-year PFS and OS for the entire cohort were 30% and 39%, respectively. Responding patients fared better than those with primary treatment failure, with 59% of CR patients event free at 4 years. Patients with AITL fared worse with an OS of 18% versus 48% for PTCL-NOS. These particularly poor results for HDT-ASCT for AITL stand in contrast to a large retrospective, multicenter study of 146 patients with AITL who had an OS of 59% at 4 years, with 4-year PFS of 56% for the subset in CR at the time of transplantation.<sup>34</sup>

In one of the larger prospective trials, the Nordic Lymphoma Group presented preliminary results of CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) given every 14 days for 6 cycles followed by HDT-ASCT for responding patients.<sup>35</sup> The majority had PTCL-

Table 1. Selected studies of high-dose therapy and autologous stem cell transplantation in peripheral T-cell lymphoma (PTCL).

Study Group/ Country	N	Med age	Risk factors	Histologies	Pre-regimens	Status	F/U mos	OS (mo)	EFS/DFS/ PFS (mo)	TRM/ NRM, %
GEL-TAMO (2003) <sup>53</sup>	115	41	AA-IPi 0-1 40% 2-3 60%	PTCL-NOS=62.6% ALCL-21.8% AITL-5.2%	Various PR/CR>1 62% Refr 6%	CR1-32%	37	56	60	8
GEL-TAMO-CR1 (2007) <sup>25</sup>	74	46	AA-IPi 2-3 65%	PTCL-NOS 50% ALCL-31% AITL-11%	CHOP-72%	CR1	67	68	63	4
BSBMT/ABMTRR (2007) <sup>26</sup>	64	45	IPI Unknown 42% 0-1 59% 2 19% 3-4 22%	ALCL-31% (+/-) PTCL-47% AITL-8%	Various	CR1-48% CR2-6%, PR-23% POD-22%	37	53	50	15
Finland (2004) <sup>27</sup>	37	46	IPI 0-1 46% 2 22% 3-4 30%	ALCL-38% PTCL-38% EATCL-14%	Various	CR/PR1-49% CR/PR2-38	24	54	46	11
Italy (2006) <sup>36</sup>	62	43	AA-IPi 0-1 29% 2-3 71%	PTCL-45% ALCL+ 30% AITL 16%	HDS MACOP-B	CR1-35 PR1-10	76	34 (21)	30 (19)	4.8
GELA (2004) <sup>54</sup>	28	36	AA-IPi 0-1 25% 2-3 75%	Non-ALCL-100%	ACVB NCVB	CR/CRu-100%	78	54	44	NR
GELCAB (2008) <sup>32</sup>	41	47	0-1 22% 2 32% 3 22% 4-5 24%	PTCL 49% AITL 29% HSTCL 5% NK nasal 5% other 12%	High-dose CHOP + ESHAP	CR/CRu 49% PR 10%	38	39	30	NR
EBMT (2008) <sup>55</sup>	146	53	NR	AITL 100%	Various	CR1 34% CR2 14% PR 36%	31	59	42	7
Nordic (2006) <sup>35</sup>	121	55	IPI 0-2 46% 3-4 54%	PTCL 41% AITL 17% Alk-ALCL 23% EATCL 12% Other 7%	CHOEP	CR/CRu 50% PR 37%	24	67	NR	4

Abbreviations: HDS, high-dose sequential therapy; ACVB, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; NCVB, mitoxantrone, cyclophosphamide, vindesine, bleomycin, prednisone; HSTCL, hepatosplenic t-cell lymphoma; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; CHOEP, CHOP plus etoposide; ESHAP, etoposide, cisplatin, cytarabine, prednisone; PTCL-NOS, PTCL-not otherwise specified; ALCL, aplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; EATCL, enteropathy-associated T-cell lymphoma; CR, complete remission; PR, partial remission; PR, partial remission; POD, progression of disease

NOS, AITL, or ALCL (ALK-1–positive ALCL patients were excluded). The median age was 55 years, and 54% had H-I or high-risk disease. Seventy-three percent (77/105) of evaluable patients responded to their initial chemotherapy and proceeded to HDT-ASCT. At a median follow-up of 24 months 67% of patients were alive. Corradini et al published updated long-term results of two Phase II studies using an approach of either multi-agent high-dose sequential therapy (HDS) or MACOP-B followed by HDT-ASCT for PTCL.<sup>36</sup> No differences in outcomes were noted between the two approaches. In an intent-to-treat analysis with a median follow-up of 76 months, estimated 12-years OS and EFS were 34% and 30%, respectively. When ALK-1-positive ALCL patients were excluded, the poorer-prognosis PTCL patients showed considerably worse outcomes, with only 18% event free at 10 years and only 21% were alive. Again, CR to induction chemotherapy at the time of transplant was prognostic with 48% of these patients alive and 47% event free compared to OS and EFS of 22% and 11%, respectively, for those not in CR. This difference was particularly striking among the PTCL-NOS patients who were event free 62% of the time if initial CR was achieved versus only 10% if it was not. This very long-term follow-up of prospectively treated patients also sheds some light on the retrospective series discussed. And the frequent late relapses raise the question as to the whether the benefits of HDT-ASCT, if they exist, may be in the form of improved PFS and delayed relapses more akin to the use of HDT-ASCT as consolidation in mantle cell lymphoma.

Recent reports suggest that allogeneic stem cell transplantation may be effective therapy, almost exclusively in the relapse setting, with clinical evidence of a graft-versus-lymphoma effect. Corradini et al reported a Phase II study of 17 patients, many of whom had previous autologous transplantation.<sup>37</sup> Excellent DFS and OS rates of 64% and 80%, respectively, were seen, with several relapsed patients responding to donor lymphocyte infusions suggestive of a graft-versus-lymphoma effect. Transplant-related mortality (TRM) was initially reported as 6%; however, an updated report with longer follow-up showed a TRM of 13%. Similar rates of disease control, although significantly higher toxicity, were reported in a large retrospective French registry series.<sup>38</sup> Seventy-seven patients with PTCL (65 had either ALCL, PTCL-NOS, or AITL) were reported, with 57 undergoing a myeloablative conditioning regimen. Only 31 were in CR at the time of allogeneic SCT. The 5-year OS and EFS rates were 57% and 53%, respectively. However, unlike the Italian study, toxicity was high with a 1-year TRM of 32% as full myeloablative conditioning was included in this series.

### New Treatments

While current salvage regimens show some promise, what is more exciting is the expanding number of new drugs

being studied specifically in PTCL. As discussed, already available drugs such as denileukin diftitox, alemtuzumab, bevacizumab, and gemcitabine are being included in combination regimens for PTCL. Other existing drugs such as bortezomib and irinotecan may have activity and are candidates for new combinations.<sup>39,40,41</sup> Other agents such as nelarabine, clofarabine, lenalinomide, and mTOR inhibitors are either being studied or have shown anecdotal activity in PTCL.<sup>42,43</sup> While these new uses of approved drugs are adding to an elongating list of useful or promising therapies for PTCL, there are currently no drugs specifically studied and approved for the treatment of PTCL. However, that may soon change as several novel agents are being developed specifically for their activity in PTCL. Pralatrexate and depsipeptide showed activity in T-cell lymphomas in early, broad, Phase I studies, and subsequent trials have built upon those early reports.

Pralatrexate is a novel antifolate designed for higher affinity for RFC-1 (reduced folate carrier) and increased polyglutamation, resulting in increased internalization and retention of the drug in tumors. Promising activity was seen in a Phase I-II trial where the first 4 patients with PTCL achieved a CR.<sup>44</sup> An expansion of this experience in 24 patients with relapsed and refractory PTCL resulted in a 50% response rate on an intent-to-treat basis, including 9 of the 16 evaluable patients with a CR.<sup>45</sup> Overall, pralatrexate was reasonably well tolerated. The dose-limiting toxicities were thrombocytopenia and stomatitis, the latter of which was largely abrogated with vitamin B12 and folic acid supplementation. A multicenter registration Phase II study of pralatrexate in relapsed or refractory PTCL has just completed enrollment. If results in this Phase II study, which includes more than 100 patients, reflect the earlier experience, pralatrexate may become the first drug to be reviewed by the FDA specifically for its activity in PTCL. Based on preclinical evidence of synergy, pralatrexate and gemcitabine are being combined in a Phase I trial.

Depsipeptide, a histone deacetylase inhibitor (HDACi), followed a similar pattern to pralatrexate with early activity seen in CTCL in a broad Phase I study.<sup>46</sup> HDACi inhibit enzymes that regulate acetylation of core nucleosomal histones as well as other proteins. The resulting increase in acetylation affects the expression of a wide range of genes, and several HDACi agents have shown promising antineoplastic effects, particularly in T-cell lymphomas. Depsipeptide's anecdotal activity in the NCI Phase I trial was followed by an NCI Phase II study showing a 28% response rate in relapsed/refractory PTCL.<sup>47</sup> A prospective multicenter Phase II trial of depsipeptide in CTCL has recently completed enrollment, and an international multicenter registration trial in PTCL is actively accruing. During the same time period, vorinostat became the first HDACi approved by the FDA for cancer treatment after a Phase II trial showing activity in patients with relapsed CTCL.<sup>48</sup> Gastrointes-

tinal side effects and thrombocytopenia were the most frequent toxicities noted in the vorinostat trials.

Beyond alemtuzumab, several novel monoclonal antibodies show some early promise in PTCL. Zanolimumab is a human monoclonal antibody that targets the CD4 antigen on normal T cells and the majority of PTCL. Phase II studies are currently ongoing in relapsed/refractory PTCL as well as CTCL. Preliminary results in 21 patients with PTCL showed a response rate of 24% without excessive infectious toxicity.<sup>49</sup> A pilot study of CHOP in combination with zanolimumab is ongoing for patients with PTCL. Other monoclonal antibodies being studied for PTCL include several anti-CD30 antibodies. CD30 is uniformly expressed in ALCL and in approximately 30% of cases of PTCL-NOS as well as Hodgkin lymphoma. Both MDX-060, a human anti-CD30 monoclonal antibody, and SGN-30, an anti-CD30 chimeric antibody, showed responses in several patients with ALCL.<sup>50,51</sup> Both were well tolerated with minimal drug-related side effects. These drugs are being modified and combined with chemotherapy in ongoing studies, primarily for Hodgkin lymphoma. Other antibodies in development include the anti-CD2, siplizumab.<sup>52</sup>

The problem of the lack of effective therapies to offer patients with PTCL is being replaced by new issues—so many drugs and new strategies are in development for these uncommon and heterogeneous lymphomas that the number of options is large as is the competition among clinical trials for patients. Fortunately, physicians and patients are becoming aware of the unique challenges of PTCL and increasingly understand that the only way to make progress is to move beyond the anecdotes and participate in well-designed prospective trials. Whether utilizing new upfront combination regimens, HDT-ASCT, or novel drugs for the still too common relapsed patients, it is only through these well-designed trials that we can move forward in an understandable way. These trials will allow us to identify the most active of the new agents and/or combinations of therapies, and ultimately move beyond CHOP as the primary therapy for patients with PTCL.

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Off-label drug use: Investigational drugs for PTCL, pralatrexate, HDACIs, monoclonal antibodies. Off-label use of alemtuzumab, clofarabine, bortezomib.

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