Management of Relapses After Hematopoietic Cell Transplantation in T-Cell Non-Hodgkin Lymphomas

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T-cell non-Hodgkin lymphomas (NHLs) are a heterogeneous group of malignancies that represent 10%–15% of all NHLs. The prognosis of relapsed T-cell NHL is poor, especially for those relapsing after an autologous (auto-) or allogeneic (allo-) hematopoietic cell transplantation (HCT). Disease relapse post auto-HCT is best managed on a clinical trial. In the absence of an investigational protocol, the choice of salvage therapies should take into account patient performance status, eligibility for an allo-HCT, and surface CD30 expression. CD30-directed therapies or aggressive salvage regimens can be used as a bridge to allo-HCT in medically fit patients. In the elderly or more infirm patients, single-agent therapies could be offered, aiming at palliation. Similarly, relapse after an allo-HCT is not uncommon and is a real challenge. Reduction in ongoing immune suppression or donor lymphocyte infusion are often considered in this setting to augment graft-versus-lymphoma (GVL) effects and can occasionally provide durable disease control. Clinical trials designed to investigate novel therapeutic agents with immunomodulatory properties to augment GVL effects (eg, histone deacetylase [HDAC] inhibitors, proteasome inhibitor, lenalidomide) or targeted therapies (eg, aurora A kinase inhibitors, anaplastic lymphoma kinase [ALK] inhibitors) are sorely needed to improve the dismal outcomes of T-cell NHL relapsing after an allo-HCT.

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T-cell non-Hodgkin lymphomas (NHLs) represent approximately 10%–15% of all NHLs in the Western countries. T The most common histological types include nodal peripheral T-cell lymphoma (PTCL), systemic anaplastic large-cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma. T The disease course in T-cell lymphomas is characterized by frequent relapses, and eventual development of refractory disease. T The prognosis of relapsed T-cell NHL is poor. In a recent study, the median overall survival (OS) and progression-free survival (PFS) of relapsed T-cell NHL were 5.5 and 3.1 months, respectively, and were only marginally better in patients who received chemotherapy at relapse (6.5 and 3.7 months, respectively). Owing to the dismal outcomes of relapsed T-cell NHL when managed with conventional chemotherapy alone, several investigators have evaluated the role of autologous (auto-) or allogeneic (allo-) hematopoietic cell transplantation (HCT) as part of the initial therapy or at the time of progression (reviewed elsewhere in the current issue of Seminars in Hematology). Unfortunately, disease relapse following HCT remains problematic, with no prospective data available to guide therapy for post-transplant relapses. Reviewed here are management options for T-cell lymphomas relapsing after either an auto- or allo-HCT. For the purposes of this review, the available therapeutic agents are arbitrarily divided into options following relapse from either an auto-HCT or an allo-HCT. While such an assignment is partly based on available data, potential biological rationale, or authors’ opinions, it is important to emphasize that the agents discussed in the post allo-HCT relapse setting could be (and often are) used in the post auto-HCT setting and vice versa. Due to the relative paucity of data regarding HCT in cutaneous T-cell lymphomas (CTCLs), readers are referred to focused reviews on novel therapeutic agents for relapsed CTCL in the current issue of Seminars.
PATIENTS AT HIGH-RISK OF RELAPSE AFTER HCT

Defining factors predicting a higher relapse risk is critical for improving HCT outcomes of T-cell NHL. Reliable identification of such “at risk” patients can potentially lead to development of personalized post-transplant maintenance and/or consolidation strategies or more vigilant surveillance in order to identify relapses early, where immune modulation or targeted therapies might have a better probability of providing disease control. Several large retrospective studies and smaller phase II trials have reported outcomes of auto- or allo-HCT for relapsed/refractory T-cell NHL. The heterogeneity of these reports in terms of the broad spectrum of histologies included and transplant procedures employed, makes reliable identification of factors associated with risk of relapse difficult. Nevertheless, it appears that the risk of disease relapse post HCT thematically follows the familiar trend for most malignancies where the patient’s performance status, depth of disease response, and tumor chemosensitivity plays a key role (Table 1). Patients with a poor performance status,5–9 high International Prognostic Index,10–14 and those not in complete remission (CR)6,11,15 or ones with refractory disease6,15,16 appear to have a higher risk of relapse. The presence of acute or chronic graft-versus-host disease (GVHD) has also been shown to be associated with a lower probability of relapse following allo-HCT.5,7

MANAGEMENT OF RELAPSE AFTER AUTOLOGOUS TRANSPLANTATION

Treatment of relapsed T-cell NHL after an auto-HCT poses a real therapeutic challenge. In this setting, salvage chemotherapy or immunotherapy, is often offered as a bridging strategy to an allo-HCT. Unfortunately, only a minority of these patients are eligible for an allograft due to various reasons including the presence of resistant disease, unavailability of a suitable donor, and suboptimal performance status or organ impairment, among others. In this section we discuss therapies with potential to bridge patients to an allo-HCT or providing disease control in a noncurative setting. It is important to emphasize that randomized data in this setting are lacking and evidence is mainly based on uncontrolled single-arm studies or small case series. The role of a second auto-HCT is unknown in T-cell lymphoma and not recommended outside the setting of a clinical trial.

Targeted Therapies

**Brentuximab Vedotin**

Brentuximab vedotin (Adcetris, Seattle Genetics, Bothell, WA) is a CD30 antibody conjugated to a potent antimicrotubule agent, monomethylauristatin E. In the United States, it is approved for the treatment of Hodgkin lymphoma after failing an auto-HCT and for relapsed/refractory ALCL.17 In a recent phase II study of patients (n = 58) with relapsed or refractory ALCL (anaplastic lymphoma kinase [ALK] negative = 72%), brentuximab showed an impressive overall response rate (ORR) of 86% (57% CR)18 (Table 2). Brentuximab was administered at a dose of 1.8 mg/kg intravenously every 3 weeks for up to 16 doses. The study included 15 (26%) patients who received a prior auto-HCT. However, the authors did not describe outcomes pertinent to this specific subgroup. The median duration of response was 13.2 months for six patients with refractory ALCL.17 In a recent phase II study of patients showing an ORR of 48%.19 Unfortunately, only one patient in this study had received a prior auto-HCT, limiting our ability to determine the efficacy of this agent in this particular setting (Table 2). Serious side effects have been described with denileukin diftitox, including fatal infusion reactions, capillary leak syndrome, and loss of visual acuity and color vision among others. The role of denileukin diftitox as a bridge to allo-HCT for CD25-expressing T-cell NHL relapsing after an autograft warrants investigation.

**Alemtuzumab**

Alemtuzumab (Campath, Genzyme, Cambridge, NJ) is an anti-CD52 monoclonal antibody approved for the treatment of persistent or recurrent CD25+ CTCL. It represents a genetically engineered recombinant DNA fusion protein that combines the enzymatically active A and B fragments of diphtheria toxin with the sequence of interleukin-2. Dang et al reported results of a multicenter phase II study in 27 subjects with relapsed/refractory T cell NHL, who had previously received more than two lines of therapies, showing an ORR of 48%.21 Unfortunately, only one patient in this study had received a prior auto-HCT, limiting our ability to determine the efficacy of this agent in this particular setting (Table 2). Major adverse events included opportunistic infections, viral reactivations, and hematologic toxicity. In the relapsed/refractory setting, alemtuzumab has also been combined with multi-agent chemotherapy regimens in a handful of small prospective studies (Table 2). The ORRs are generally modest (~30%–50%) and the remissions do not appear to be durable.23,24 Given that only 30%–40% of PTCLs express CD52,25,26 it is not known if restricting alemtuzumab to CD52+ T-cell lymphomas would provide more durable remissions. The ongoing randomized ACT-1 trial (www.clinicaltrials.gov; NCT00646854) is comparing
## Table 1. Factors Predicting a Higher Risk of Relapse Following Hematopoietic Cell Transplantation

<table>
<thead>
<tr>
<th>First Author (year)</th>
<th>No. of Patients (histology)</th>
<th>Transplant Type</th>
<th>Conditioning Regimen</th>
<th>Risk Factors Predicting Relapse Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodríguez (2007)</td>
<td>123 (T-cell NHL)</td>
<td>Autologous-HCT</td>
<td>BEAM, BEAC or CY/TBI</td>
<td>High IPI and β₂-microglobulin associated with greater risk of progression</td>
</tr>
<tr>
<td>Mercadal (2008)</td>
<td>45 (T-cell NHL)</td>
<td>Autologous-HCT</td>
<td>BEAM or BEAC CY/TBI</td>
<td>High IPI score associated with inferior outcomes</td>
</tr>
<tr>
<td>Reimer (2009)</td>
<td>83 (T-cell NHL)</td>
<td>Autologous-HCT</td>
<td>CY/TBI</td>
<td>Patients not in complete remission and those with high PIT score had inferior outcomes</td>
</tr>
<tr>
<td>Yang (2009)</td>
<td>64 (T-cell NHL)</td>
<td>Autologous-HCT</td>
<td>-</td>
<td>High IPI, PIT score, and LDH associated with greater risk of progression</td>
</tr>
<tr>
<td>Nademanee (2011)</td>
<td>67 (T-cell NHL)</td>
<td>Autologous-HCT</td>
<td>TBI-based or BEAM</td>
<td>High PIT score associated with higher risk of relapse</td>
</tr>
<tr>
<td>d’Amore (2012)</td>
<td>160 (T-cell NHL)</td>
<td>Autologous-HCT</td>
<td>BEAM or BEAC CY/TBI</td>
<td>Advanced age, bone marrow involvement, poor performance status and non-ALCL histology associated with greater risk of progression</td>
</tr>
<tr>
<td>Le Gouille (2008)</td>
<td>77 (all subtypes)</td>
<td>Allogeneic-HCT</td>
<td>RIC = 20</td>
<td>Refractory disease associated with higher risk of relapse</td>
</tr>
<tr>
<td>Kyriakou (2009)</td>
<td>45 (AITL)</td>
<td>Allogeneic-HCT</td>
<td>MA = 57 RIC = 25</td>
<td>Chronic GVHD associated with reduced risk of relapse</td>
</tr>
<tr>
<td>Dodero (2012)</td>
<td>52 (PTCL)</td>
<td>Allogeneic-HCT</td>
<td>MA = 20 RIC = 52</td>
<td>Refractory disease and &gt;2 lines of prior therapy associated with higher risk of relapse</td>
</tr>
<tr>
<td>Kanakry (2013)</td>
<td>44 (T-cell NHL)</td>
<td>Allogeneic-HCT</td>
<td>RIC = 24</td>
<td>Acute and chronic GVHD associated with reduced risk of relapse</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALCL, anaplastic large T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; AITL, angioimmunoblastic T-cell lymphoma; BEAM, carmustine, etoposide, cytarabine, cyclophosphamide; BEAC, carmustine, etoposide, cytarabine, melphalan; CY/TBI, cyclophosphamide/total body irradiation; HCT, hematopoietic cell transplantation; IPI, International Prognostic Index; MA, myeloablative conditioning; PIT, Prognostic Index for PTCL; PTCL, peripheral T-cell lymphoma; RIC, reduced-intensity conditioning.
<table>
<thead>
<tr>
<th>First Author</th>
<th>Targeted Therapy</th>
<th>Antibody Dose/Schedule</th>
<th>N1</th>
<th>N2</th>
<th>Histology</th>
<th>Response</th>
<th>Survival (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro(^{18})</td>
<td>Brentuximab Vedotin</td>
<td>1.8 mg/kg every 3 wk (up to 16 doses)</td>
<td>58</td>
<td>15</td>
<td>ALCL</td>
<td>ORR = 86(^{*})</td>
<td>PFS = 13.3 mo</td>
</tr>
<tr>
<td>Gibb(^{19})</td>
<td>Brentuximab Vedotin</td>
<td>1.8 mg/kg capped at 100 kg every 3 wk</td>
<td>24</td>
<td>8</td>
<td>HL = 18</td>
<td>ORR = 88(^{*})</td>
<td>PFS = 5.1 mo</td>
</tr>
<tr>
<td>Dang(^{21})</td>
<td>Denileukin diftitox</td>
<td>18 µg/kg/d ×5 d every 3 wk</td>
<td>27</td>
<td>1</td>
<td>T-cell NHL</td>
<td>ORR = 48(^{*})</td>
<td>PFS = 6 mo</td>
</tr>
<tr>
<td>Enblad(^{22})</td>
<td>Alemtuzumab</td>
<td>30 mg, 3 times/wk x 12 wk</td>
<td>14</td>
<td>-</td>
<td>T-cell NHL</td>
<td>ORR = 36%</td>
<td>Median duration of response was 6 mo</td>
</tr>
<tr>
<td>Weidman(^{24})</td>
<td>Alemtuzumab + FCD</td>
<td>10 mg on day 1, and 30 mg on d 2–3 of each cycle</td>
<td>11</td>
<td>0</td>
<td>T-cell NHL</td>
<td>ORR = 55%</td>
<td>PFS = 2.5 mo</td>
</tr>
<tr>
<td>Kim(^{23})</td>
<td>Alemtuzumab + DHAP</td>
<td>70 mg or 40 mg/cycle divided over 3 d</td>
<td>24</td>
<td>0</td>
<td>T-cell NHL</td>
<td>ORR = 50%</td>
<td>OS = 6.1 mo</td>
</tr>
<tr>
<td>Ishida(^{27})</td>
<td>KW-0761</td>
<td>1.0 mg/kg/wk x 8 wk</td>
<td>28</td>
<td>-</td>
<td>ATLL</td>
<td>ORR = 50(^{*})</td>
<td>PFS = 5.2 mo</td>
</tr>
</tbody>
</table>

\(^{*}\)All treated subjects.  
\(^{†}\)Responses for previously autografted patients only.  
Abbreviations: N1, Total number of patients; N2, number of patients who had a prior autologous transplant; ORR, overall response rate; CR, complete remission; DoR, median duration of objective response; PFS, progression-free survival; OS, overall survival; HL, Hodgkin lymphoma; ATLL, adult T-cell leukemia/lymphoma; ALCL, anaplastic large cell lymphoma; T-cell NHL, T-cell non-Hodgkin lymphoma; AILT, angioimmunoblastic T-cell lymphoma; DHAP, dexamethasone, cytarabine, cisplatin; FCD, fludarabine, cyclophosphamide, doxorubicin (Campath-FCD).
chemotherapy alone with alemtuzumab plus chemotherapy in patients with PTCL. Given the frequency of infectious complication and modest efficacy data, alemtuzumab should be not be used outside of a clinical trial in T-cell lymphomas.

**KW-0761**

CC chemokine receptor 4 (CCR4) is expressed by tumor cells in adult T-cell leukemia/lymphoma (ATLL) and has emerged as a potential target for therapy. KW-0761 (mogamulizumab) is a new humanized anti-CCR4 monoclonal antibody with a defucosylated Fc region that enhances antibody-dependent cellular cytotoxicity. Ishida et al recently reported a multicenter phase II study in 28 ATLL patients, who had failed at least one previous chemotherapy regimen. ORR was 50%, including eight CRs (Table 2). This targeted therapy warrants further investigation in ATLL and other T-cell lymphomas.

**Conventional Single-Agent Chemotherapy**

**Gemcitabine**

Single-agent gemcitabine (Gemzar, Eli Lilly, Indianapolis, IN) is active in relapsed T-cell lymphomas. In a single-institution phase II study, 39 patients with relapsed/refractory PTCL (n = 20) or CTCL (n = 19) received gemcitabine 1,200 mg/m² on days 1, 8, and 15 of a 28-day cycle. ORR in PTCL patients was 55% (30% CR). Five of six PTCL cases remained in continuous CR at a median of 34 months (range, 5–60), suggesting that sustainable responses are possible. Single-agent gemcitabine is an attractive therapy option for T-cell NHL patients who are unfit for allo-HCT (especially those lacking surface CD30 expression). Gemcitabine-based combinations are also feasible as discussed below.

**Pralatrexate**

Pralatrexate (Folotyn, Allos Therapeutics, Westminster, UK) is a folate analog metabolic inhibitor currently approved for the treatment of relapsed or refractory PTCL. The landmark PROPEL study evaluated the efficacy of pralatrexate (30 mg/m²/wk for 6 weeks followed by 1 week of rest) in 111 relapsed/refractory PTCL patients, with a median age of 58 years. Vitamin B₁₂ 1,000 μg intramuscularly every 8–10 weeks and folic acid 1–1.25 mg/d were required to be administered alongside pralatrexate. Treatment was continued until evidence of disease progression, development of unacceptable toxicity, or physician discretion. Eighteen (16%) patients had received a prior auto-HCT, and six (33%) demonstrated an objective response to pralatrexate. The median duration of response was 10.1 months in all responders. Severe mucositis was common (any grade = 71%, grade III–IV = 22%). Pralatrexate demonstrates efficacy in relapsed/refractory T-cell NHL, but the durability of responses in previously autografted subjects is not known. Nonetheless, it represents a reasonable option for T-cell NHL relapsing after an auto-HCT. In the elderly or infirm patients, a lower-dose pralatrexate regimen (15 mg/m², 3 weeks on/1 week off) is active (ORR = 45%) and better tolerated.

**Pixantrone**

A novel aza-anthracenedione, pixantrone dimaleate has demonstrated improved efficacy (CR 20% v 5.7%; P = .021) in patients with relapsed/refractory aggressive NHLs when compared with other chemotherapeutic agents in a recently published phase III trial. Unfortunately, only six (PTCL = 3, ALCL = 3) (8.6%) of 70 patients with T-cell lymphomas received pixantrone dimaleate, limiting our ability to determine the efficacy of this agent in this particular setting.

**COMBINATION CHEMOTHERAPY REGIMENS**

Combination chemotherapy regimens are best reserved for medically fit, younger patients requiring effective cytoreduction before a potential allo-HCT.

**Gemcitabine-Based Combinations**

Gemcitabine has shown activity in combination with other antineoplastic agents. Arkenau et al reported a regimen combining gemcitabine (1,000 mg/m² on days 1, 8, and 15), cisplatin (100 mg/m² on day 15), and methylprednisolone (1000 mg/d for 5 days) in 16 patients with T-cell lymphomas. ORR was 69% (19% CR). The median time to disease progression was 123 (range, 0–288) days and OS was 68.2%. The main grade 3/4 toxicities were hematologic (leucopenia = 62%). The combination of gemcitabine (1,000 mg/m² on day 1), oxaliplatin (100 mg/m² on day 1), and dexamethasone (20 mg/d for 4 days) is also active in previously treated T-cell lymphomas (ORR = 38%, CR = 8%). Gemcitabine-based chemotherapy regimens represent a reasonable option to cytoreduce patients before a planned allo-HCT. Prior reports of serious pulmonary toxicity with gemcitabine and CD30 antibody (SGN30) combination will likely preclude prospective investigation of gemcitabine and brentuximab–containing regimens.

**Other Combinations**

The group in Princess Margaret Hospital recently reported a retrospective analysis of 40 patients, median age of 53 years, with relapsed/refractory PTCL. Most patients (>70%) were treated with DHAP (cisplatin, cytarabine, and dexamethasone) or ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) as salvage chemotherapy, with an ORR of 62%. The proportion of
patients who proceeded to receive an auto-HCT was 55%. This study demonstrates activity of DHAP or ESHAP in relapse/refractory PRCL; however, its specific efficacy in the setting of post auto-HCT relapse remains to be determined. Several other chemotherapy combination regimens have been evaluated in the treatment of relapsed/refractory T-cell lymphomas. Mikesch et al retrospective compared DexaBEAM (dexamethasone, Carmustine, etoposide, cytarabine, and melphalan) and ICE (ifosfamide, carboplatin, and etoposide) in relapsed/refractory T-cell lymphomas. The investigators reported higher ORR (69% v 20%), CR (38% v 7%), and PFS (6.4 v 2 months, P = .01) with DexaBEAM. However, treatment associated toxicities were also seen more frequently with DexaBEAM. Several limitations ought to be taken into account when interpreting these results, including the retrospective nature of the analysis and the small sample size.

T-cell NHL relapsing after an auto-HCT is best managed on prospective clinical trial designed to assess the activity of novel agents (or combinations) in this high-risk patient population. In the absence of an investigational protocol, the choice of salvage regimen should take into account patient performance status, donor availability, suitability for an allo-HCT, and surface CD30 expression. Brentuximab is an attractive (and perhaps preferred) option for CD30-expressing T-cell NHL, particularly for ALCL. Combination chemotherapy regimens are best reserved for medically fit patients, as a bridge to an allo-HCT, while for the elderly or infrim patients single-agent chemo- or immunotherapy with a palliative intent or supportive/end-of-life care options should be kept in mind.

MANAGEMENT OF RELAPSE AFTER ALLOGENEIC TRANSPLANTATION

Allo-HCT is a potentially curative modality for relapse/refractory T-cell NHL; however, approximately 25%–35% of allografted patients ultimately relapse. Management of relapsed T-cell NHL after allo-HCT is challenging for several reasons: first, a large proportion of these patients have a performance status unsuitable for aggressive salvage therapies, second; ongoing myelosuppression, delayed immune reconstitution, GVHD, and compromised organ function often coexist in this population, magnifying the adverse events of therapies tolerated in other settings, and third; these patients are frequently excluded from available clinical trials. No prospective studies are available to guide therapy in this setting. In the following sections we discuss risk factors associated with post allo-HCT relapse, available strategies to augment graft-versus-lymphoma (GVL) effects and review novel therapeutic agents that either have immunomodulatory properties (to support their application in post allo-HCT setting) or an adverse event profile feasible for a frail post allo-HCT patient.

Immunosuppression Withdrawal and Donor Lymphocyte Infusions

Augmentation of GVL effects, either by tapering immune suppression (IS) or by the administration of donor lymphocyte infusion (DLI), can provide durable disease control in a subset of patients relapsing after allo-HCT. In the absence of active and severe GVHD, reduction or withdrawal of immunosuppressive medications (if present), is generally considered a first step in managing post allo-HCT relapses in hematologic malignancies, and has anecdotally shown sustained remissions in a handful of T-cell NHL patients. For patients who are not on IS at the time of disease relapse, and in those where tapering IS does not induce a potent GVL effect, DLI is (if available) could be explored and have shown efficacy in small case series. Dodero et al administered DLI to 12 T-cell NHL patients relapsing after allo-HCT. Eight patients responded, including five CRs. Median survival of patients achieving a CR following DLI was 5 years, with no subsequent relapse reported. Itonaga et al performed DLI in nine ATLL patients. Four patients achieved a CR, but only two survived disease-free long-term. While DLI appears feasible in relapsed T-cell NHL, no randomized data are available to guide whether it is best administered alone, or following cytoreductive (chemo- or radio-) therapies. The optimal CD3+ cell dose, product type (cryopreserved cells v fresh cytokine-stimulated cells v fresh unstimulated cells), and interval between DLI infusions are not well defined. Limitations of DLI include development of GVHD and requirements for previously cryopreserved cells or donor availability to procure a fresh leukapheresis product. For obvious reasons, DLI is not an option for post cord blood transplant relapses.

Recommendations

Acknowledging the lack of quality prospective data, withdrawal of post allo-HCT IS is (if present) for relapsed T-cell NHL (in the absence of severe active GVHD) is a reasonable first step. In patients who are not on IS or where reducing IS is unsuccessful, consideration should be given to DLI. In patients with widespread, organ-threatening or bulky relapse, DLI is best administered after cytoreductive systemic therapies or involved-field radiation.

Aurora-A Kinase Inhibitor

Alisertib (MLN8237) is an oral investigational agent that inhibits Aurora A Ser/Thr kinase. It inhibits proliferation, promotes endo-reduplication and induces apoptosis in T-lymphoma cell lines, supporting its role in PTCL. Preliminary results of a phase II clinical trial of alsertib in relapsed B- and T-cell NHL, showed encouraging signal of activity in PTCLs with 57% of patients responding (Table 4). Toxicities were mild and included
<table>
<thead>
<tr>
<th>First Author (year)</th>
<th>Histology</th>
<th>Total No. of Patients</th>
<th>No. Intervened (IS withdrawal or DLI)</th>
<th>Response to Intervention</th>
<th>Duration of Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Withdrawal of IS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Hamadani (2008)40    | T-cell NHL | 14                    | 2                                   | CR = 2                  | —                    | • Retrospective  
  • Authors stated prolonged response, but did not specify duration  
| Itonaga (2013)6      | ATLL      | 35                    | 20                                  | CR = 2                  | 46+ mo               | • Retrospective  
  • 8 developed GVHD  
| Corradini (2004)41   | T-cell NHL | 17                    | 3                                   | CR = 1                  | 17+ and 28+ mo       | • Retrospective |
| **DLI**              |                                      |                                     |                        |                        |                      |          |
| Le Gouill (2008)6    | T-cell NHL | 77                    | 2                                   | CR = 2                  | 2+ yr                | • Retrospective  
| Kyriakou (2006)5     | AITL      | 45                    | 2                                   | CR = 2                  | 14+ and 74+ mo       | • Retrospective  
| Dodero (2012)16      | T-cell NHL | 52                    | 12                                  | CR = 5                  | All PR patients progressed | • Retrospective  
| Itonaga (2013)8      | ATLL      | 35                    | 9                                   | CR = 4                  | 2 alive in CR at 48+ and 69+ mo | • Retrospective  
  • 6 developed GVHD  
  • 6 died due to progression  
  • 1 died due to infections  
|                     |                                      |                                     |                        |                        | PR = 1  
  NoR = 1 |

**Abbreviations:** ATLL, adult T-cell leukemia/lymphoma; AITL, angioimmunoblastic T-cell lymphoma; CR, complete remission; DLI, donor lymphocyte infusion; GVHD, graft-versus-host disease; IS, immune suppression; NHL, non-Hodgkin lymphoma; NoR, no response; PR, partial remission.
Table 4. Agents With (potential) Activity in T-Cell NHL Relapsing After Allogeneic Transplant

<table>
<thead>
<tr>
<th>First Author (year)</th>
<th>Therapeutic Agent &amp; Study Design</th>
<th>Histology</th>
<th>Total No. of Patients</th>
<th>No. Post allo-HCT/allo-HCT Excluded?</th>
<th>Response Rate</th>
<th>Duration of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedberg (2011)</td>
<td><strong>Alisertib</strong></td>
<td>T-cell NHL</td>
<td>8</td>
<td>0/Excluded</td>
<td>ORR = 57%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>Damaj (2013)</td>
<td><strong>Bendamustine</strong></td>
<td>T-cell NHL</td>
<td>60</td>
<td>NR/NoC</td>
<td>ORR = 50%</td>
<td>Median 3.5 mo</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
<td>CR = 28%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR = 22%</td>
<td></td>
</tr>
<tr>
<td>Dueck (2010)</td>
<td><strong>Lenalidomide</strong></td>
<td>T-cell NHL</td>
<td>24</td>
<td>3/Not excluded</td>
<td>PR = 31%</td>
<td>Median 96 d</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Uike (2012)</td>
<td><strong>Lenalidomide</strong></td>
<td>T-cell NHL</td>
<td>13</td>
<td>NR/NoC</td>
<td>ORR = 31%</td>
<td>Median 280 d</td>
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<tr>
<td>Lee (2008)</td>
<td><strong>Bortezomib + CHOP</strong></td>
<td>T-cell NHL</td>
<td>13</td>
<td>NR/NoC</td>
<td>ORR = 61.5%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Phase I</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Evens (2011)</td>
<td><strong>Bortezomib + gemcitabine</strong></td>
<td>T-cell NHL</td>
<td>16</td>
<td>NR/NoC</td>
<td>ORR = 25%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Phase I/II</td>
<td></td>
<td></td>
<td></td>
<td>CR = 19%</td>
<td></td>
</tr>
<tr>
<td>Tan (2012)</td>
<td><strong>Bortezomib + panobinostat</strong></td>
<td>T-cell NHL</td>
<td>11</td>
<td>NR/NoC</td>
<td>ORR = 54.5%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Pohlman (2009)</td>
<td><strong>Belinostat</strong></td>
<td>T-cell NHL</td>
<td>20</td>
<td>NR/NoC</td>
<td>CR = 18%</td>
<td>Median 6 mo</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
<td>ORR = 25%</td>
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<tr>
<td>Piekarz (2011)</td>
<td><strong>Romidepsin</strong></td>
<td>T-cell NHL</td>
<td>47</td>
<td>18*/Not excluded</td>
<td>ORR = 38%</td>
<td>Median 8.9 mo</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
<td>CR = 18%</td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>PR = 20%</td>
<td></td>
</tr>
<tr>
<td>Coiffier (2012)</td>
<td><strong>Romidepsin</strong></td>
<td>T-cell NHL</td>
<td>130</td>
<td>0/Excluded</td>
<td>ORR = 25%</td>
<td>Median 17 mo</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
<td>CR = 15%</td>
<td></td>
</tr>
</tbody>
</table>

*Number includes patients undergoing autologous transplantation.
Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete remission; NHL, non-Hodgkin lymphoma; NR, not reported; NoC, not clear from the publication; ORR, overall response rate; PR, partial remission.
leukopenia, fatigue, and diarrhea. Alisertib’s oral bioavailability, favorable toxicity profile, and efficacy make it an ideal investigational candidate for post allo-HCT maintenance or treatment of relapsed T-cell NHL. A phase III clinical trial comparing alisertib against investigator’s choice of chemotherapy is ongoing, but unfortunately excludes patients with a prior allo-HCT (NCT01482962).

**Histone Deacetylase Inhibitors**

Histone deacetylase (HDAC) inhibitors are epigenetic therapies that induce acetylation of histones and other proteins, resulting in antitumor activity due to increased tumor-suppressor gene transcription, growth inhibition, cell cycle regulation, and apoptosis. Romidepsin (Istodax; Celgene, Summit, NJ), a potent, bicyclic class I selective HDAC inhibitor, is approved for relapsed CTCL and PTCL. In the two published phase II studies romidepsin therapy in relapsed/refractory T-cell NHL showed promising activity (response rates = 25%–38%), with median duration of response ranging from 9–17 months. Common toxicities were nausea, fatigue, and transient cytopenias. Romidepsin and other HDAC inhibitors with activity in T-cell NHL are summarized in Table 4. In addition to their activity in T-cell NHL, HDAC inhibitors have also been shown to prevent acute GVHD disease by reducing proinflammatory cytokines, modulating antigen-presenting cell function, and increasing regulatory T cells. These data suggest the feasibility of administering HDAC inhibitors post allo-HCT. Since romidepsin is approved for relapsed T-cell NHL, it represents a reasonable therapeutic option for such patients relapsing after an allograft.

**Bendamustine**

Bendamustine (Treanda; Teva, Frazer, PA) a bifunctional alkylating agent approved for patients with CLL and indolent B-cell NHL, has only partial cross-resistance to other alkylating agents. In a recently published phase II clinical trial, single-agent bendamustine showed promising activity (Table 4) in relapsed/refractory PTCLs, with an encouraging safety profile. While efficacy data for T-cell NHL relapsing after allo-HCT are not available, bendamustine’s single-agent activity in PTCL and favorable toxicity profile makes it an attractive agent to investigate in often frail patients relapsing after an allo-HCT, potentially as a cytoreductive therapy before a planned DLI.

**Lenalidomide**

Lenalidomide (Revlimid; Celgene, Summit, NJ) is an immunomodulatory agent with several potential mechanisms of action, including direct cytotoxicity, enhanced natural killer/T-cell function, and alternation of microenvironment. In addition to its known activity in multiple myeloma (MM) and myelodysplastic syndrome (MDS), limited data also suggest that lenalidomide is active in T-cell NHL (Table 4). The overall response rates with lenalidomide in the two published studies were approximately 30% with thrombocytopenia being the most frequently encountered adverse event. Investigation of lenalidomide as an immunomodulatory agent in T-cell NHL relapsing after allo-HCT is particularly attractive, since administration of lenalidomide to MM, or MDS patients after allo-HCT has been shown to augment graft-versus-malignancy effects, supported by induction of GVHD and concurrent disease responses in several patients. However, owing to the risks of inducing severe GVHD, lenalidomide administration to T-cell NHL relapsing following an allo-HCT should be limited to well-designed prospective trials.

**Crizotinib**

Crizotinib (Xalkori; Pfizer, Mission, KS) an oral inhibitor of ALK, is active in ALK-expressing non-small cell lung cancers. Approximately 50% of ALCL patients are ALK-positive, and potentially represent an area where the role of targeted therapy with crizotinib warrants investigation. This agent has shown dramatic activity in three cases of relapsed ALK-positive ALCL, with two patients achieving durable remissions. Several ongoing early-phase clinical trials are investigating the role crizotinib in relapsed/refractory ALK-positive ALCL (NCT00939770, NCT01606878, NCT01524926), including two studies that are also enrolling ALCL relapsing after an allo-HCT (NCT01606878, NCT01524926).

**Bortezomib**

Bortezomib (Velcade; Millennium, Cambridge, MA), a dipeptide boronic acid that selectively and potently inhibits the proteasome 26S complex, is approved for MM and mantle cell lymphoma. It induces apoptosis in T-lymphoma cell lines, and downregulates positive regulatory domain I–mediated chemoresistance in human T-NHL cells. Bortezomib in combination with other therapeutic agents has shown activity (response rates ranging from 25%–60%) in relapsed/refractory T-cell NHL (Table 4). However, no studies focusing on role of bortezomib in T-cell NHL relapsing after allo-HCT are available. Bortezomib’s activity in T-cell NHL, and its recently shown efficacy in preventing acute GVHD, warrant evaluating the role of bortezomib maintenance or consolidation after allo-HCT in T-cell lymphomas.

**Other Options for Post Allo-HCT Relapse**

A myriad of other therapeutic agents are in clinical trials for patients with relapsed T-cell NHL, including monoclonal antibodies (eg, sipilizumab [anti-CD2], zanolimumab [anti-CD4], LMB-2 [anti-CD25]),
Figure 1. Practical approach towards a T-cell lymphoma patient relapsing after an autologous transplant (auto-HCT).

Figure 2. Practical approach towards a T-cell lymphoma patient relapsing after an allogeneic transplant (allo-HCT). DLI = donor lymphocyte infusion; GVHD = graft-versus-host disease.
Management of relapses after HCT in T-cell NHL

The use of peripheral blood grafts, growth factor administration, improved human leukocyte antigen (HLA)-typing techniques, and modern supportive measures have undoubtedly improved the safety of transplantation, disease relapse post HCT in T-cell NHL remains a challenge. This is an exciting time for developmental therapeutics in T-cell NHL, with several agents showing promising activity. While the routine use of peripheral blood grafts, growth factor administration, improved human leukocyte antigen (HLA)-typing techniques, and modern supportive measures have undoubtedly improved the safety of transplantation, disease relapse post HCT in T-cell NHL remains a challenge. This is an exciting time for developmental therapeutics in T-cell NHL, with several agents showing promising activity. Moving forward, efforts ought to be focused on evaluating novel consolidation or maintenance strategies post auto- or allo-HCT, especially in patients at higher risk of relapse. Trials evaluating the role of maintenance with immunomodulatory agents (eg, lenalidomide; NCT01035463) post auto-HCT are ongoing. In the post allo-HCT relapse setting strategies to activate donor T-cells by administrating an anti-CTLA4 antibody, ipilimumab (Yervoy; Bristol-Myers Squibb, New York, NY) are being investigated (NCT01822509). An ongoing Southwest Oncology Group study (S1106) is evaluating role of alisertib in relapsed T-cell NHL. Rationally designed clinical trials employing novel agents against unique targets in malignant T cells or tumor microenvironment (eg, mTOR/AKT/P13K pathways, ALK protein, surface antigen, etc), will be the key for improving the dismal outcomes of T-cell NHL relapsing after HCT.

REFERENCES


49. Tan D, Hwang W, Dione C, et al. Bortezomib (BTZ) and panobinostat (PAN) combination is effective in patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) or NK/T-cell lymphoma (NKBL) and maintenance treatment may be essential for sustained response. ASH Annual Meeting Abstracts. 2012;120:3669.