Review: Clinical Trial Outcomes

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Questions for stem cell transplant in peripheral T-cell non-Hodgkin's lymphomas

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Peripheral T-cell lymphomas (PTCL) are distinct entities as compared to B-cell lymphomas and carry worst outcomes. Stem cell transplantation has been used to treat these diseases but the exact role for this therapeutic modality is not fully defined for PTCL. Autologous stem cell transplants have been used to consolidate an upfront remission in PTCL with improved disease outcomes though most patients eventually relapse. High-dose therapy and stem cell transplant can also salvage some patients in the relapsed setting if they have chemosensitive disease. Nodal histologies like anaplastic large cell lymphoma, angioimmuoblastic T-cell lymphoma and PTCL-not otherwise specified seem to benefit the most from these approaches. Allogeneic stem cell transplantation has been used to harness the graft versus lymphoma effect to provide long-term disease control in relapsed PTCL and may be curative. Improved targeted T-cell directed therapies have allowed more PTCL patients to reach transplantation thus improving overall outcomes for these diseases.

Keywords: allogeneic stem cell transplant • autologous stem cell transplant • peripheral T-cell lymphoma • PTCL • stem cell transplant

Mature T-cell non-Hodgkin lymphomas (NHL) arise from post-thymic T cells that have populated the peripheral lymphoid organs, collectively referred to as peripheral T-cell lymphomas (PTCL) and including natural killer (NK)/T-cell lymphomas (TCL) arising from NK cells and their subtypes. The current 2008 WHO classification of hematopoietic and lymphoid neoplasms recognizes 20 types of mature T- and NK-cell neoplasms and three provisional entities [1]. PTCLs can be classified based on the site of origin of the lymphoma. The most common nodal histologies are peripheral TCL-not otherwise specified (PTCL-NOS), anaplastic large-cell lymphoma (ALCL), and angioimmunoblastic TCL (AITL). The extranodal variants include the nasal and extranasal NK/TCL, hepatosplenic TCL (HSTCL), the enteropathy-associated TCL and the subpanniculitis T-cell lymphoma. A leukemic presentation is seen in human T-lymphotropic virus type I-associated adult T-cell leukemia/lymphoma (ATLL), prolymphocytic T-cell lymphoma. Cutaneous TCL (CTCL) represent a clinically distinct subgroup of T-cell NHL, generally with a more indolent behavior, with the exception of a few subtypes including Sézary syndrome and transformed mycosis fungoides that have a more aggressive course and decreased survival [2]. While most histologies are considered aggressive with a 5-year survival rate of less than 30%, the most aggressive histologies include ATLL, HSTCL, γ/δ T-cell malignancies and NK/TCLs with worse outcomes. T-cell phenotype tends to confer poorer clinical outcomes than does B-cell phenotype, with the exception of ALK-positive (ALK^+) ALCL [3,4]. Advanced disease stage, high prognostic index at presentation and inherent chemo-resistance contribute to the unsatisfactory outcomes for this disease group. Since PTCL-related disorders are characterized by

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rarity, marked heterogenicity in histologies and biologic behavior, the management recommendations are mostly based on small retrospective clinical studies as well as borrowed paradigms from treatment of aggressive B-cell malignancies. Since 2009 there are three agents that have now been approved by the US FDA for the treatment of PTCL in the relapsed setting and this includes pralatrexate [5], romidepsin [6] and brentuximab vedotin [7] for relapsed systemic ALCL. There are no approved agents for the upfront treatment of PTCL.

Stem cell transplants for PTCL

There is an extensive body of literature dealing with the topic of transplantation for PTCL particularly in the last 10 years. Starting with case reports, and retrospective data analysis, there is now a clear shift towards designing and conducting prospective trials and to look at specific questions in offering stem cell therapy to patients with PTCL. However, there is still a lack of randomized trials and several questions remain to be answered.

One approach fits all is not appropriate for the treatment of PTCL and this applies to transplant options as well. Treatment recommendations are based upon retrospective data, Phase II data and personal experiences. However, the ongoing recognition of the varying biologic features of the various subtypes of PTCL and the differences in geographic distribution of these disease has led to studies of specific subtypes in areas of prevalence like ATLL and NK/TCLs in Japan and Korea as well as the Carribean as seen in the literature in the last 5 years. This will only continue to evolve over time and as newer targeted agents become available, they will be incorporated into these treatment paradigms.

Autologous transplants for PTCL

Currently, high-dose therapy and stem cell transplantation is considered in patients with PTCL who may achieve a complete remission (CR) or partial response (PR) after primary therapy and who may be candidates for this approach based on age and other comorbid conditions [8]. The practice of consolidating a remission state achieved after induction therapy has been extrapolated from the treatment of acute leukemia where primary therapy is not expected to cure the disease. In terms of lymphoid malignancies, high-dose chemotherapy and autologous stem cell transplantation (ASCT) in first remission after primary therapy has been shown to improve overall survival (OS) and progression free survival (PFS) for mantle cell lymphoma and multiple myeloma. For PTCL, this recommendation excludes ALK^+ ALCL, and CTCL. It is recognized that ALK^+ ALCL has an excellent prognosis as compared with other types of PTCL including ALK-negative (ALK^-)ALCL with overall response rates of over 90%, a 5-year relapse-free survival of 60% and a 5-year OS of 70% with standard CHOP-based chemotherapy. The addition of stem cell transplantation is not likely to improve these results significantly [9]. Additionally, brentuximan vedotin targeting CD30 and agents targeting ALK can provide excellent responses in the relapsed setting thus eliminating the need for an aggressive approach in first CR. The caveats to this rule including patients with a high International Prognostic Index (IPI) score or elderly patients over the age of 60 years who have a worse prognosis and may be considered for stem cell transplantation in first CR. CTCLs are a group of PTCL that are considered to have a more indolent course with many relapses and even spontaneous remissions with the exception of primary cutaneous γ/δ T-cell lymphoma. Most patients will enjoy a long course with the use of only skin directed therapies and may not require any systemic therapy or chemotherapy for a long period of time. Very aggressive variants of PTCL, including human T-lymphotropic virus type I-associated ATLL, the extra nasal NK/TCLs, T-cell prolymphocytic leukemia (T-PLL) and the HSTCL and the primary cutaneous γ/δ T-cell lymphoma, have been shown to have a very aggressive clinical course due to inherent chemoresistance and there are multiple failures with primary therapy. Long-term remissions and improved survival have been seen in patients undergoing an allogeneic transplant in first remission where possible [10].

Randomized trials for autologous stem cell transplants

The only randomized trials looking at the role of high-dose therapy and ASCT in TCLs were performed in the late 1990s and were designed to study the questions in aggressive lymphomas that included TCLs. In LNH-87–2, 452 patients with high-risk lymphoma were identified and those who achieved CR were randomized to either a consolidation regimen of aggressive combination therapy or high-dose chemotherapy and ASCT [11]. A total of 17% of the patients had a T-cell phenotype. In this trial, the high-dose arm was shown to have a better outcome as compared with the consolidation arm with an 8-year disease-free survival (DFS) of 55 versus 39% and OS of 64 versus 49%. In LNH-93, 370 patients were enrolled and 22.7% had a T-cell phenotype [12]. The authors compared the standard induction and consolidation regimen prevalent at that time to a shortened induction and ASCT consolidation with a BCNU, etoposide, cytarabine, melphalan (BEAM)-based ASCT within 60 days of completing chemotherapy. This trial reported an inferior outcome of the transplant arm; 5-year OS of 60 versus 46%, and EFS of 46 versus 39%. In 2004, the data from both GELA trials was pooled for all subtypes of NHL to see if there was a benefit to high-dose

therapy and ASCT in first CR [13]. There were 51 (16%) patients with TCLs including precursor TCLs and ALK$^+$ ALCL. In conclusion, no benefit could be demonstrated by this approach for PTCL. However it is difficult to apply this interpretation to current practice as the trials were not designed to look specifically for PTCL and included aggressive histologies like lymphoblastic lymphoma. Additionally, patients received intensification and consolidation which is not the standard practice anymore.

Prospective trials for autologous stem cell transplants

There are now six reported prospective trials for using high-dose therapy and ASCT performed in first CR for primarily nodal PTCL in transplant eligible young patients (Table 1). In all trials, transplant eligible patients were induced with chemotherapy and those who achieved a CR or PR were offered high-dose therapy with ASCT, with the intention of answering the following questions: While individual trials had differing study points, all were designed to address the role of high-dose therapy and ASCT as consolidation of first remission in patients with PTCL in order to improve the outcome of these patients.

The Nordic Lymphoma group has reported the largest multicenter trial to date and has specifically looked at the intensity of the induction regimen as well as the effect of ASCT in responding patients [14]. This is the only study that is large enough to provide meaningful information regarding the histologic subtypes of the common nodal PTCLs. A dose dense combination of cytoxan, adriamycin, vincristine, etoposide and prednisone, given every 14 days was chosen as the induction regimen. Etoposide was omitted for the 42 patients over the age of 60 years, thus providing a cohort of patients for comparison to see if the addition of etoposide made a difference in outcome. In this study, patients were removed from the study for stable disease (SD) or progressive disease (PD). All transplanted patients received a uniform nonradiation based conditioning regimen of either (BEAM or BCNU, etoposide, cytarabine, cytoxan [BEAC]). A total of 131 patients had a CR, complete remission unconfirmed or PR to initial therapy with an overall response rate (ORR) of 82%. A total of 25 patients were primary refractory and were taken off and another 16 patients could not proceed to transplant due to failure to mobilize stem cells, other medical reasons or disease progression. In total, 114 (71%) patients underwent ASCT and 90 patients (78% of those transplanted) were in CR at 3 months post-transplant. There were 39 relapses post-transplant. The majority of the relapses (n = 28; 18% of transplanted patients) were in the first 2 years of transplant and the remaining 11 were late relapses as late as 71 months post-transplant. Transplant-related mortality (TRM) was 4% (n = 7). At a median of 60 months of follow up, 83 patients were alive, OS 51% and DFS 44% (entire cohort). The 5-year OS of the patients who did not undergo transplantation was 28% compared with 61% of the cohort that underwent ASCT. In a subset analysis, the best outcomes were seen in patients with ALK$^-$ ALCL. For the over 60 years of age cohort, the ORR was 88% (55% CR and 33% PR), 5 years OS of 45% and DFS of 34%. These results were similar to the group that received etoposide with ORR of 84% (50% CR, 34% PR), 5-year OS of 40% and DFS of 39%. Female sex, and ALCL histology had a positive prognostic value and IPI had a predictive value for OS in AITL and for PFS in AILT and PTCL-NOS. Bone marrow involvement and increasing age were negative prognostic factors. This study indicates that upfront transplantation improves outcome of OS and EFS compared with historical controls. The results of this study are superior to other previous studies indicating that a more dose-dense schedule may improve the upfront results allowing more patients to proceed to transplant. However about a quarter of the patients failed initial therapy and could not proceed to transplant. This behooves the need for more aggressive and perhaps targeted therapies to improve the initial response rate and perhaps reduce the number of early relapses. The late failure pattern of some of these patients makes an argument that there is a need to better define this subset perhaps through some form of MRD follow-up and offer maintenance therapy to this subset. D'Amore *et al.* [14] and Januten *et al.* [15] have reported subset analysis of this study in specific histological subtypes of ALK$^-$ ALCL and enteropathy-associated TCL, respectively, with a 3-year OS of 64 and 40% for the two histologies.

Reimer *et al.* have reported the German data on 83 patients and also concluded that there was a positive impact on outcome using the upfront auto ASCT approach [16]. All patients were treated with standard CHOP therapy and assessed for response after 4 cycles. Patients with PD or SD were taken off study. The conditioning regimen was radiation based with TBI and cytoxan. Of the 83 patients, 73 completed CHOP therapy with an ORR of 79% (39% CR + 40% PR). A total of 24 patients did not proceed to transplant. At the time of transplant there were 59 responders but only 55 patients actually went to transplant. By intent to treat analysis only 66% of the patients completed the protocol. There were 22 relapses after the transplant with a median time to relapse of 11.5 months (2–46 months). In an intent to treat study, the ORR was 66% (58% CR and 8% PR). In a subgroup analysis the estimated OS of patients undergoing ASCT was 71% compared with 11% for the nontransplant group. This group of 28 patients

Table 1. Prospective studies of high-dose therapy and autologous stem cell transplant in peripheral T-cell lymphomas.

Study (year)	Subjects (n)	Histology	Median age (years)	Induction	Response at transplant	Conditioning	Transplanted by ITT (%)	OS	EFS	Comments	Ref.
D'Amore *et al.* (2012)	160	Excluded ALK$^+$ ALCL	57 (18–67)	CHOEP 14 × 3 for age <60 years, CHOP 14 for age >60 years	CR1 or PR ORR: 82%	BEAM/BEAC	72	5-year OS: 51%	5-year PFS: 44%	ALCL OS: 70%; PFS: 61%; AILT OS: 52%; PFS: 49%; PTCL-NOS 5-year OS: 47%; PFS: 38%; EATL 5-year OS: 48%; PFS: 38%	[14]
Reimer *et al.* (2009)	83	Non-ALK$^+$ ALCL	NR	CHOP (4–6 cycles)	CR or PR n = 55 66%	TBI/Cy	66	48% (3 years)	36% (3 years)	High PIT score associated with worse OS (p = 0.04) 34% of patients in the original cohort had PD	[16]
Corradini *et al.* (2006)	62	Included ALK$^+$ ALCL (30%)	NR	Combination chemotherapy		BEAM	71	34% (12 years)	55% (12 years)	Results better for ALK$^+$ ALCL; high IPI and failure to achieve CR were poor prognostic factors	[17]
Ahn *et al.* (2011)	46	25% had NK/TCL exclude ALK$^+$ ALCL	NR	CHOP, CHOP-like or non-nanthracyclin	CR: 51%	Bu/CY/VP-16	67	57% (5 years)	55% (5 years)	NR	[61]
Mercadal *et al.* (2008)	41	Exclude ALK$^+$ ALCL	NR	High-dose CHOP alternating with ESHAP	CR1: 49%	BEAM/BEAC	41	39% (4 years)	30% (4 years)	IPI had prognsotic significance	[19]
Reimer *et al.* (2007)	26	Exclude ALK$^+$ ALCL	NR	Mega CHOP, if PR or SD after 3 cycles got IFE	CR or PR	BEAM	73	73% (3 years)	53% (3 years)	Chemosensitive disease had better outcome	[16]

AILT: Angioimmunoblastic T-cell lymphoma; ALCL: Anaplastic large-cell lymphoma; BEAC: BCNU, etoposide, cytarabine and cytoxan; BEAM: BCNU, etoposide, cytarabine and melphalan; Bu/CY/VP-16: Busulphan, cytoxan and etoposide; CHOEP: Cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone; CHOP: Cytoxan, adriamycin, vincristine and prednisonel; CR: Complete remission; Cy: Cytoxan; EATL: Enteropathy-associated T-cell Lymphoma; EFS: Event-free survival; ESHAP: Etoposide, methylprednisone, cytarabine and cisplatin; IFE: Ifosfamide and etoposide; IPI: International Prognsotic Index; ITT: Intent to treat; NK: Natural killer; NOS: Not otherwise specified; NR: Not reported; ORR: Overall response rate; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PIT: Prognostic Index for peripheral T-cell lymphoma; PR: Partial remission; PTCL: Peripheral T-cell lymphoma; SD: Stable disease; TBI: Total body irradiation; TCL: T-cell lymphoma.

had a median OS of 8 months with 23 patients dead at the time of last follow up. TRM of the whole course was 3.6%. Univariate analysis indicated that there was significant correlation between the prognostic index for T-cell lymphoma (PIT) score and OS. A low IPI score and a CR at the time of transplantation showed a non-significant trend towards a longer OS. As compared with the later published Nordic lymphoma study [14], this study has an inferior outcome for similar histologies of PTCL which may be attributed to a less dose-dense induction therapy resulting in fewer patients making it to transplant. The conditioning regimen was radiation based in the German study which did not seem to increase the TRM in this study. The median follow up was short and a long-term plateau in the survival and DFS curves could not be demonstrated due to early relapses within 2 years.

Corradini *et al.* reported the pooled Italian experience from two separate centers. In total there were 62 patients, but this cohort included patients with ALK$^+$ ALCL constituting about 30% of the patients [17]. The induction regimen was intense in both studies and involved multiple agents. In total, 16 out of 62 (26%) patients did not proceed to ASCT, whilst 46 (74%) proceeded to a BEAM-based ASCT and were followed for over 6 years (median 73 months). TRM was 4.8%. At the end of ASCT, 41 of 46 patients (89%) were in CR with no difference in the two treatment protocols. In total, 14 patients relapsed after ASCT. At a median follow up of 76 months (15–140 months) 30 of 62 patients (48%) were alive. The estimated 12-year OS was 34%, DFS was 55% and EFS was 30%. Since these studies included patients with ALK$^+$ ALCL that has a better prognosis in all PTCL subtypes, this may have skewed the results. When compared with other cohorts, ALK$^+$ ALCL patients had better outcomes with OS at 62 versus 21%, and EFS of 54 versus 18%. For the subgroup of PTCL the 12-year OS and EFS was 37 and 25% respectively. In these studies CR/PR prior to transplant and IPI score was found to impact survival in PTCL-NOS. This study concluded that achievement of CR before autografting was a strong predictor of survival and that ALK$^+$ ALCL seemed to have the best outcome with this approach. Hwang *et al.* reported on a cohort where 25% of the patients had NK/T-cell lymphoma. Initial therapy was CHOP based and 33% did not make it to transplant [18]. Mercadal *et al.* also reported on PTCL patients treated in a prospective manner with combination chemotherapy that were added on to a back bone of CHOP based therapy [19]. Both studies excluded the good prognosis ALK$^+$ ALCL and responding patients went on to BEAM/BEAC based transplants. Intent to treat analysis revealed that only 41 and 73% of the original cohort made it to transplant respectively. IPI and chemosensitive disease predicted for improved outcome.

These studies show that in the appropriate patients with PTCL, the initial chemosensitive response to primary therapy can be deepened by high-dose therapy and ASCT in appropriate patients. The problem remains twofold:

- A median age of presentation in the mid sixties for most histologies, most patients with PTCL may not be transplant candidates due to co morbid conditions;
- Approximately a half to a third of the patients do not achieve an adequate state of remission with primary therapy to proceed to a consolidative transplant.

Retrospective trials for autologous stem cell transplant

Over the past 20 years or so there have been over 24 studies that have looked at the role of ASCT for PTCL. Compared to the prospective data, the retrospective studies have an inherent selection bias in terms of favoring patients who are younger and are able to undergo transplant. Transplants have been carried out in patients with relapsed disease for salvage, or to consolidate a remission including a first or subsequent remission. These studies have included patients with active or refractory disease unlike prospective studies that excluded patients who progressed or even had SD indicating chemoresistance. Overall the studies have looked at the outcomes of approximately 1400 PTCL patients over a time span of over 17 years at various major cancer centers throughout the world. In general these studies are heterogeneous in terms of patient populations, upfront treatment regimens, conditioning regimens and follow-up care. Based on their description, almost all of them exclude patients with leukemic variants of PTCL including Sezary syndrome and ATLL as well as indolent forms of CTCL and are limited to otherwise healthy and younger patients with median ages less than 60 years based on institutional standards. These studies are useful in understanding the role of high-dose therapy (HDT) and ASCT transplant for PTCL. The data from these has been summarized in Table 2.

Feasibility of high-dose therapy & ASCT for PTCL

In 1999, Fanin *et al.* looked at the outcomes of 64 patients with only CD30 positive T- and null-cell ALCL based on REAL classification in various European Bone Marrow Transplantation centers and concluded that the 15 patients who received a transplant in CR1 had a long-term survival of over 90% and may have been cured in keeping with their earlier anecdotal observations [20]. This was the first suggestion that HDT/ASCT may provide long-term survival if performed in CR1 in certain histologies of PTCL.

Table 2. Retrospective studies of high-dose therapy and autologous stem cell transplant in peripheral T-cell lymphomas.

Study (year)	Subjects (n)	Median age (years)	Histologies	Disease status at transplant	Median follow up	OS	PFS/DFS	TRM	Comments	Ref.
Beitinjaneh *et al.* (2011)	126	49	PTCL: 42; ALCL: 47; ALK$^+$: 7; AITL: 15; NK/T cell: 6; HSTCL: 6	CR/PR: 84%; Relapse: 16%; CR1: 33% CR2: 67%	39 months	39% (4 year) For CR1: 87% (4 years)	30% (4 year) For CR1: 67% (4 year)	3%	Best outcome in CR1 and PTCL-NOS	[22]
Mak *et al.* (2013)	38 (Allo: 17; auto: 21)	62.5	PTCL-NOS, ALCL, AILT (n = 45)	Transplanted in CR2: 100%	4 year	55% (3 year)	48% (3 years)	NR	No difference in outcome for auto vs allo Survival: 5.4 months for those who were not transplanted	[62]
Nademanee *et al.* (2011)	67	48	ALCL: 30 (16% ALK$^+$); PTCL-NOS: 30; AITL: 7	CR/PR: 70% Transplanted in second-line induction failure: 82% (n = 20)	65.8 months	54% (5 years) For CR1: 75 vs 32%	40% (5 years) For CR1: 92 vs 45%	6.3% (1 year)	High PIT score predicted for a poor outcome, relapse rate higher for transplants beyond CR1	[24]
Prochazka *et al.* (2011)	Auto: 19; Allo: 2 (in CR1)	NR	NR	Consolidated in CR1	NR	65% (2 years)	EFS: 52% (2 years)	NR	PET negativity after initial therapy associated with improved outcome Higher OS and EFS with low or intermediate IPI 77 and 64%	[34]
Hwang *et al.* (2011)	35 (Allo: 5; auto: 25)	NR	PTCL-NOS: 25; NK/T cell: 10	CR/PR: 74%	NR	PTCL-NOS: 76% (5 years) NK/TCL: 53% (5 years)	NR	NR	Multivariate analysis showed remission status only prognostic factors for OS	[18]
Numata *et al.* (2010)	39	NR	23% ALCL ALK$^+$	CR/PR: 82% Transplanted first line: 59%	78 months	62% (5 years)	PFS 61%: (5 years)	NR	Age and disease status impacted survival	[25]
Yang *et al.* (2009)	64	NR	PTCL-NOS	CR1: 16; PR1: 12; PD: 6	29.7 months	53% (3 years)	EFS: 44% (3 years)	NR	Failure to achieve CR and PIT of 2–3 poor prognostic factors	[63]
Nickelsen *et al.* (2008)	424	51 (17–74)	ALCL: 9; ALK$^+$: 19; PTCL-NOS: 176; AITL: 120; Aggressive others: 30	CR1: 35% CR/PR beyond CR1: 52%	3 years	49% (3 years)	62% (3 years)	NR	Poor PS, age over 60 years, chemosensitive disease beyond CR1, PTCL-NOS were adverse factors.	[21]

AITL: Angioimmunoblastic T-cell lymphoma; ALCL: Anaplastic large-cell lymphoma; CR: Complete remission; CTCL: Cutaneous T-cell lymphoma; DFS: Disease-free survival; DLBCL: Diffuse large B-cell lymphoma; EATL: Enteropathy-associated T-cell Lymphoma; EFS: Event-free survival; HSTCL: Hepatosplenic T-cell lymphoma; NK: Natural killer; NOS: Not otherwise specified; NR: Not reported; OS: Overall survival; PD: Progressive disease; PET: Positron emission tomography; PFS: Progression-free survival; PIT: Prognostic index for T-cell lymphoma; PR: Partial remission; PS: Performance status; PTCL: Peripheral T-cell lymphoma; SD: Stable disease; TCL: T-cell lymphoma; TRM: Treatment-related mortality; U: Unspecified.

Table 2. Retrospective studies of high-dose therapy and autologous stem cell transplant in peripheral T-cell lymphomas (cont.).

Study (year)	Subjects (n)	Median age (years)	Histologies	Disease status at transplant	Median follow up	OS	PFS/DFS	TRM	Comments	Ref.
Chen *et al.* (2008)	53	NR	ALK$^+$ ALCL: 34%	CR/PR1: n = 15 CR2/PR2: n = 26 Refractory disease: n = 19 CR/PR: 81%	5 years	48% (5 years) CR1/ PR1: 87%; CR/ PR2: 40%; Refractory: 30%	PFS 25% (5 years); CR1/PR1: 51%; CR2/ PR2 12%; Refractory diseae: 0	NR	Best results for transplant in CR1/PR1 86% had a T-cell depleted graft	[41]
Smith *et al.* (2007)	32	NR	ALK$^+$ ALCL: 66%	CR/PR: 74% Second-line: 81%	30 months	34%	18%	NR	No advantage for transplants in first remission	[32]
Feyler *et al.* (2007)	64	NR	PTCL-NOS: 34; ALCL: 20; Included CTCL, precursor neoplasms ALK$^+$ ALCL: 31%	CR/PR: 78% Second line: 72%	37 months from transplant	53% (3 years) CR1: 59% (2 years) vs CR2/PR2/SD: 49% (2 years) vs refractory: 37% (2 years)	PFS: 50% (3 years) vs CR2/PR2/SD: 50% (2 years) vs refractory: 34% (2 years)	NR	PTCL-NOS, chemosensitive disease impacted OS and DFS	[45]
Kim *et al.* (2007)	40	NR	PTCL-U: 20; Extra noda NK/T cell 10; ALCL: 5; AITL: 3; Rare: 2	CR: 27% PR: 53%	16 months	11.5 months, OS of transplanted patients has not been reached	EFS: 3.6 months	NR	CR status at the time of transplant impacted EFS and OS	[26]
Kewalramani *et al.* (2006)	24	NR	Chemosensitive relapse or RD	NR	6 years	24% (5 years)	33% (5 years)	NR	Outcome similar to DLBCL OS of 34% and EFS of 39% in relapsed and refractory DLBCL	[43]
Jantunen *et al.* (2004)	37	NR	PTCL-NOS: 14; ALCL; 14; EATL: 5; Others: 4 CR1/PR1: 18; CR/ PR2: 14	NR	24 months	5-year OS is 54%	NR	11%	ALCL had superior survival, best outcomes in early transplants in first remissions	[30]

AITL: Angioimmunoblastic T-cell lymphoma; ALCL: Anaplastic large-cell lymphoma; CR: Complete remission; CTCL: Cutaneous T-cell lymphoma; DFS: Disease-free survival; DLBCL: Diffuse large B-cell lymphoma; EATL: Enteropathy-associated T-cell Lymphoma; EFS: Event-free survival; HSTCL: Hepatosplenic T-cell lymphoma; NK: Natural killer; NOS: Not otherwise specified; NR: Not reported; OS: Overall survival; PD: Progressive disease; PET: Positron emission tomography; PFS: Progression-free survival; PIT: Prognostic index for T-cell lymphoma; PR: Partial remission; PS: Performance status; PTCL: Peripheral T-cell lymphoma; SD: Stable disease; TCL: T-cell lymphoma; TRM: Treatment-related mortality; U: Unspecified.

Some of the larger studies with over 50 patients have been reported in the last 10 years either from large cancer centers or combined multicenter studies that reflect the practice patterns of their individual institutions.

The largest study to date was presented at ASH 2008 [21]. Niclelsen *et al.* reported the data from over several European Bone Marrow Transplantation registry centers in Europe that performed high-dose therapy and ASCT for PTCL from 2000 to 2005 [21]. The large US cancer centers as well as the Spanish, Italian, Japanese and Korean centers, have all reported on the outcomes of ASCT in PTCL and the data that are summarized in Table 2 [22–26]. All these studies confirm that HDT/ASCT is feasible in patients with PTCL and there is an experience in all disease states; that is, first or subsequent remission, PR or CR, SD as well as refractory disease. Where possible, there has been an attempt to look at the effect of histology to see if there is any difference in outcome especially for patients with ALCL that is supposed to have a better outcome as compared with other histologies. The longest follow up has been up to 5 years and the reported 5-year median OS varies from 34 to 70% and the EFS is between 30 and 61%. However, higher OS and EFS have been reported if transplants are performed in first remission with reports of up to 80% 5-year OS and 67% EFS. Chemosensitive disease and ALCL histology seems to give better outcomes in several studies. The use of HDT/ASCT can salvage approximately a third of patients with relapsed chemosensitive disease again with the best outcomes for ALCL particularly if ALK^+. In most studies the outcome for refractory or chemoresistant disease remains dismal with less than 15% long-term survivors.

Treatment-related mortality

There are reports of TRM ranging from 3.7 to 7.5% [22,27]. The highest TRM at 11% was reported by Jantunene *et al.* in a study of 37 patients [28]. The differences in outcome may be due to the differences in reported patient groups, differing treatments and indeed differing patterns of supportive care. Some studies have a higher percentage of patients with relapsed and refractory disease who are heavily pretreated contributing to a higher TRM. It is conceivable that the use of more targeted and biologic therapies for PTCL will improve the status of patients entering into transplant therapy and improve the overall outcome. No information is available from these studies about long-term complications. The maximum follow up is up to 5 years.

Conditioning regimens

Most common nonradiation-based regimens were BEAM, BEAC, cytoxan, etoposide and BCNU, as well as a few busulphan, cytoxan (Bu/Cy), and some combinations of these agents and most patients were treated with nonradiation-based regimens. BEAM was used for over 200 patients and seemed to be the most commonly used regimen. A fair number of patients also received total body irradiation (TBI)-based regimens usually in combination with cytoxan or etoposide or both. City of Hope reported on 41 patients treated on the TBI-based regimens versus seven patients on nonradiation based-regimens and the outcomes were comparable to other studies [24]. TRM was 6.3% in this study. The choice of conditioning regimen appears to be determined by the transplant physician with no specific conditioning regimens that are recommended for PTCL.

Effect of histologic subtype

Some studies have focused on specific histological subtypes. Many retrospective studies have suggested that the outcome is better for ALCL both in the upfront setting and relapsed disease as compared with non-ALCL histology. These include Nickelsen *et al.* [21], Jagasia *et al.* [29], Jantuene *et al.* [30], Blystad *et al.* [27]. This was confirmed by statistical analysis. Other studies have shown no effect of histology which may be a function of patient selection as ALCL patients tend to have a better prognosis with upfront therapies. Zamfokk *et al.* focused on ALK^- ALCL patients only [31] and Smith *et al.* had a high percentage of relapsed ALK^+ ALCL in their series and yet reported poor outcomes with transplant [32].

European Bone Marrow Transplantation Registry has focused on the outcomes of patients with AITL only in a large cohort of 146 patients [33]. Out of 146 patients, 101 (69.2%) were transplanted in CR1 and after a median follow up of 31 months, 48% of patients were alive. The 2- and 4-year OS was 67 and 59%, respectively, and PFS was 53 and 42%, respectively. Patients who were transplanted in CR1 did better with a 4-year PFS of 56 versus 30%. Patient who had relapsed disease at the time of transplant had a 4-year PFS of 23%. High-dose therapy and ASCT seems to benefit patients with AITL in CR1. NK/TCL is more common in the far East and Hwang *et al.* reported on ten patients with NK/TCL as part of their 35 patient cohort of PTCL [18]. For NK/TCL, the 5-year OS was 53% for patients undergoing stem cell transplant in CR/PR. Some patients received allogeneic transplants and there was no reported difference in outcome. However, patients transplanted in a non-CR/PR state had a 5-year OS of only 20%.

Prognostic factors

There is no real consensus on prognostic factors though most studies have looked at many factors by both univariate and multivariate analysis. Most of

the smaller studies predicted for better outcomes for chemosensitive disease, first CR/PR and ALCL histology. Amongst the larger studies CR > 1, poor performance status, age more than 60 years and PTCL-NOS histology seemed to predict for poor outcome [21]. Gel–TAMO found that with multivariate analysis only lactate dehydrogenase predicted for survival [23]. City of Hope reported on prognostic outcomes of PTCL-related transplants and found that the PIT score predicted for outcome [24,34]. Prochazka *et al.* was the only study that looked at the prognostic value of using a PET scan to predict response [34]. A total of 12 patients had a PET scan at diagnosis and after treatment and having a negative PET scan before transplant predicted for better outcome in this small group of patients.

■ Optimal salvage regimens

From these studies, no conclusions can be drawn about the optimal salvage regime to be used at the time of transplant. Most physicians use combination chemotherapy regimens used for salvage in B-cell lymphomas without much supportive data for the efficacy of these regimens in PTCL. There is one report of the efficacy of ifosphamide, carboplatin and etoposide (ICE) in the relapsed setting of PTCL as a retrospective analysis reporting an ORR of 54% in PTCL versus 72% in B-cell lymphomas [35]. A recently published retrospective study from Germany suggests that the use of dexa BEAM (dexamethasone, BCNU, etoposide, cytarabine and melphalan) produced higher response rates of 69% with higher CRs at 38 versus 20% ORR and 7% CRs with ICE in 30 patients. The 3-year OS of the whole cohort of patients undergoing transplants was 50% [36]. Gemcitabine based regimens like Gem Ox (dexamethasone, gemcitabine and oxaliplatin) [37] are being used as salvage regimens for relapsed PTCL though there is no randomized data to support the use of one over the other. Since chemosensitive disease seems to predict for improved outcomes both for OS and PFS, it would seem that improving salvage regimes using novel and targeted agents will be the optimal way to improve the outcome for PTCL transplants. Based on recent data, agents such as brentuximab vedotin [38], pralatrexate [39] and romidepsin [40] have shown significant single-agent activity in the relapsed setting for PTCL even in heavily pretreated patients and have served as a bridge to transplant for responding patients. The current question remains if aggressive combination chemotherapy regimens such as ICE, DHAP or ESHAP are needed for salvage prior to transplant, as suggested by the current practice for B-cell lymphomas or if similar or better response rates can be obtained with single agent or targeted therapies. The future use of novel targeted therapy combinations is likely to replace the more toxic chemotherapy salvage regimens.

■ Graft modification or manipulation for autologous transplants

The group from Stanford has looked at the effect of T-cell depletion where 86% of the 53 patients received a depleted graft [41]. In this study there were 36 patients with relapsed disease and even though outcome was influenced by disease status at the time of transplant, there was no effect of graft manipulation. Similar results were reported by Nademanee *et al.* from City of Hope [24].

■ ASCT for T cell versus Diffuse large B-cell lymphoma

In 1990, Vose *et al.* first described the differences in outcome of ASCT performed in the relapsed setting for the T-cell phenotype versus B cells in aggressive lymphomas [42]. In this study, there were 17 T-cell and 24 B-cell patients based on immunophenotype and the authors did not find any difference in outcome in the two major subgroups in terms of OS and EFS, that is, at 2-year the OS was 35% for T cells and 30% for B cells, and DFS of 28 versus 17% for B cell. Numata *et al.* also compared the 5-year survival data of PTCL patients transplanted in CR/PR1 to patients with Diffuse large B-cell lymphoma (DLBCL) in CR or PR at the time of transplantation during this time period and found the results to be comparable [25]. For T-cell patients the 5-year OS and EFS was 45 and 42% for chemosensitive relapsed disease, respectively [25]. Kewalramini *et al.* also compared the results of their 24 T-cell patients to the 84 DLBCL patients in their database who also underwent transplant for relapsed disease [43]. For PTCL and DLBCL the 5-year OS was 33 and 39%, and DFS was 24 and 33%, respectively; and these results were not statistically different. Jagasia *et al.* looked at the 28 PTCL patients and compared the outcome to 84 patients with DLBCL who had a 3-year OS and DFS of 36 and 28%, respectively [29]. They concluded that ALCL patients had a superior OS as compared with DLBCL, that is, 86 versus 36% but the other histological subtypes of PTCL had comparable outcomes to DLBCL, that is, 47 versus 36% and ALK$^+$ ALCL had the best outcome.

Conclusions regarding autologous transplants

HDT and ASCT can improve outcomes if performed in a state of first remission This has been shown in studies by Beitinjaneh *et al.* [22], Kyriakou *et al.* for AITL [44], Nadamanee *et al.* [24], Numata *et al.* [25], Feyler *et al.* [45], Kim *et al.* [26] and Kewalramini *et al.* [43].

This approach can salvage approximately a third of relapsed PTCL patients if they have chemosensitive disease an outcome that at least by historical controls is similar to the outcome of relapsed DLBCL. Most common histologies seem to be PTCL-NOS and ALCL. While this data seems encouraging at first glance, this strategy is not able to salvage patients who have chemorefractory PD. Reimer *et al.* reported that a high PIT score is associated with a poor outcome indicating that advanced stage disease may not benefit from salvage ASCT [16]. Almost all studies have shown that failure to achieve remission prior to transplant portends a poor prognosis.

Allogeneic transplants for PTCL

In the field of PTCL, the rationale for allogeneic transplants has been borrowed from the paradigm of treating aggressive and intermediate grade B-cell lymphomas with the intent of invoking a graft-versus-lymphoma effect to provide long-term disease control. It has been used in the setting of relapsed or refractory disease, though transplant physicians have been using this modality in the upfront setting for particularly aggressive histologies like the γ/δ T-cell lymphomas or extranasal NK/T-cell lymphomas. This is supported by case studies and retrospective analysis of databases and one small prospective study from Italy. These consist of patients with nonuniform histologies, conditioning regimens and graft-versus-host disease (GVHD) prophylaxis. This experience is summarized in Table 3.

Is there a graft versus lymphoma effect for PTCL

The justification of performing an allogeneic transplant in PTCL can be made if a graft versus lymphoma effect can be demonstrated. In general the proof for a graft versus tumor effect can be deduced if:

- Long-term EFS and DFS can be demonstrated after reduced intensity conditioning regimens;
- DFS can be obtained even in chemorefractory patients;
- EFS correlates with the incidence of GVHD;
- Remission can be induced after histologically documented disease relapse with donor lymphocyte infusions (DLI).

For PTCL, the incidence of a graft versus lymphoma effect was effectively demonstrated in the Corradini study of 17 patients who received a reduced intensity regimen for their conditioning [46]. All patients received similar de-bulking chemotherapy with cisplatin, dexamethasone and cytarabine for four to six cycles and underwent a reduced intensity allogeneic transplant following conditioning with fludarabine, thiotepa and cyclophosphamide. The patients on this study were heavily pretreated, including eight out of 17 patients with a prior ASCT. After a median follow up of 28 months, the 3-year OS and DFS was 81 and 62%, respectively. The non-relapse mortality was 6%. This study established that reduced-intensity conditioning (RIC) can be used in PTCL with good long term outcome implicating a graft-versus-TCL effect. The largest study to date includes 77 patients reported by Le Gouill *et al.* [47]. This study is large enough to look at the differences in the common histological subtypes of PTCL in the context of an allogeneic stem cell transplant. All patients had relapsed disease and about 25% of the patients had failed a prior transplant indicating that this was a heavily pretreated population. In total, 70% of patients had chemosensitive disease at the time of transplant, 67% had an ablative conditioning regimen and a third received a RIC. The treatment related mortality was high at 33% and the 5-year OS and DFS was 57 and 53%, respectively. This is the only study that has reported differences in outcomes based on histology with 5-year OS and PFS rates of 80 and 80% for AITL, 63 and 58% for PTCL and 55 and 48% for ALCL, respectively. The 5-year OS for other histopathologic subtypes was 33%. There was a plateau in OS and PFS after 20 months. The 5-year OS of 29% even for chemoresistant patients is encouraging and supports a graft-versus-lymphoma effect. By multivariate analysis grade III and IV acute GVHD and chemoresistant disease were negative prognostic factors. In this study, GVHD did not correlate with EFS. Several centers have reported on the results of reduced intensity conditioning [48,49] with a decrease in TRM to around 19–20% as compared with the earlier reports of up to 30%. City of Hope compared the outcome using RIC versus fully ablative conditioning and found no differences in OS and DFS [50]. The use of reduced intensity conditioning has decreased TRM but the improvement in OS has not been clearly delineated, due to increased relapse rates.

The use of DLI to induce remission for relapsed disease after allogeneic transplant is considered to validate a graft-versus-disease effect and there are reports in the literature to support this for PTCL. The largest experience is from Dodero *et al.* where eight out of 12 patients with documented relapse responded to DLI and achieved a state of remission [51]. There were two patients in the Le Gouill series [47], two in the Corradini series [46], and one out of two in the Goldberg series [52] who responded to DLI after disease relapse and had a long remission. Zain *et al.* reported that there was a suggestion that in the small series, GVHD correlated with PFS [53].

Table 3. Allogeneic transplants for peripheral T-cell lymphomas.

Study (year)	Histology	Disease status	N	Conditioning	Graft source	GVHD prophylaxis	Toxicity	Response	Ref.
Perales *et al.* (2012)	PTCL	Relapsed	34	MAC TBI: 47% Chemotherapy only: 16% RIC: 38%	Peripheral blood: 71% BM: 24% Double cord: 6%	T-cell depleted: 47%	TRM: 18% Ac GVHD: 41% Ch GVHD: 25%	2-year OS: 61% 2-year PFS: 50% Plateau at 28 months, k_i-67 < 25% and CR at time of transplant	[52]
Dodero *et al.* (2012)	Nodal PTCL	Relapsed	52	RIC DLI: 8/12 relapsed pts	HLA-matched sibling: 33 Unrelated: 13 Haploidentical: 6	T-cell depletion: 22 No T-cell depletion: 30	NRM: 9% Ac GVHD: 22% Ch GVHd: 27% After DLI Ac GVHD: 31% Ch GVHD: 47%	5-year OS: 50% 5-year PFS: 40% 8/12 achieved remission after relapse with DLI	[51]
Shustov *et al.* (2010)	NR	CR1: 3 relapsed	17	RIC TBI + Flu	MR: 7 MUD: 10	CSA + MMF Tac + MMF No T-cell depletion	NRM: 19% Ac GVHD: 65% Ch GVHD: 53%	OS: 59% (at 3 years) PFS: 53% (at 3 years)	[48]
Zain *et al.* (2010)	PTCL/CTCL	CR: 7 (CR1: 3; CR2: 4) Relapsed: 12 Induction failure: 17 Prior ASCT: 1	37	RIC: 24 MAC: 13 (radiation-based: 12)	Sibling: 26 MUD: 11	CSA + MMF: 20 Tac/Sir: 17	Ac GVHD: 51.4% Ch GVHD: 82.1% TRM: 29%	Median f/u: 60.5 months for surviving patients 5-year OS: 54.4% PFS: 46.5%	[53]
Deloukina *et al.* (2011)	PTCL/CTCL	CR1, CR2/PR: 10 Relapse/ refractory: 17 Chemosensitive: 16	27	RIC only	Siblings: 15 MUD: 12	CSA+ MMF: 9 Tac/Sir: 18	Ac GVHD: 48% Ch GVHD: 71% NRM: 25%	OS: 55% (at 2 years) PFS: 47% (at 2 years) RR: 29% (at 2 years)	[54]
Le Gouill *et al.* (2008)	PTCL	CR: 31 PR: 23 PD/refractory: 23 70% were in chemosensitive relapse	77	2/3 ablative (66% rad-based) 1/3 RIC BM: 52 PB: 24 Cord: 1	Related: 60 MUD: 17	CSA + MTX based on 66% of cases	TRM: 33% (at 5 years)	5-year OS: 57% 5-year DFS: 53% TRM: 33%	[47]
Rodriguez *et al.* (2006)	PTCL	Multiply relapsed	11	RIC: 7 MAC: 4	NR	CSA + MTX	Ac GVHD: 45% Ch GVHD: 72%	2-year f/u OS and PFS RIC: 57% MAC: 50%	[50]

Ac: Acute; AILD: Angioimmunoblastic lymphadenopathy; ASCT: Autologous stem cell transplantation; BM: Bone marrow; Ch: Chronic; CR: Complete remission; CSA: Cyclosporine; CTCL: Cutaneous T-cell lymphoma; DLI: Donor lymphocyte infusion; Ext: Extensive; Flu: Fludarabine; f/u: Follow-up; GVHD: Graft-versus-host disease; HLA: Human leukocyte antigen; MAC: Myeoablative conditioning; MMF: Mycophenolate mofetil; MR: Matched related; MRD: Matched related donor; MTX: Methotrexate; MUD: Matched unrelated donor; NHL: Non-Hodgkin's lymphoma; NK: Natural killer; NR: Not reported; NRM: Non-relapse mortality; OS: Overall survival; PB: Peripheral blood; PBSC: Peripheral blood stem cells; PD: Progressive disease; PFS: Progression free survival; PR: Partial remission; PTCL: Peripheral T-cell lymphoma; pts: Patients; RIC: Redcued intensity conditioning; RR: Relapse rate; Sir: Sirolimus; Tac: Tacrolimus; TBI: Total body irradiation; TRM: Transplant-related mortality.

Table 3. Allogeneic transplants for peripheral T-cell lymphomas (cont.).

Study (year)	Histology	Disease status	N	Conditioning	Graft source	GVHD prophylaxis	Toxicity	Response	Ref.
Corradiani *et al.* (2004)	PTCL Relapsed: 15 Refractory: 2 8 (47%) failed ASCT	CR: 2 PR: 13 PD: 1 Relapse: 1	17	RIC/Thiotepa/ Flu/Cy	Siblings: 16 MUD: 1	CSA + MTX 3 pts also had alemtuzumab	Ac GVHD: 35% Ch GVHD: 50% TRM: 6%	3-year OS: 81% DFS: 62% 2 responded to DLI	[46]
Kim *et al.* (2006)	T-cell NHL NK/T-cell NHL	Multiply relapsed	54	MAC	NR	NR	NR	PTCL 5-year OS: 70% NK/TCL: 30%	[26]
Murashige *et al.* (2005)	NK/T-cell	Chemosensitive: 12 Chemorefractory: 16	28	MAC: 23 RIC: 5	MRD: 22 PBSC: 22 BM: 8	NR	Ac GVHD: 12/28 Ch GVHD: 8/17 TRM: 30%; RIC: 20%	2-year PFS: 34% OS: 40%	[58]
Suzuki *et al.* (2006)	NK/T-cells	CR: 15	15	Radiation-based MAC	NR	NR	NR	No difference in OS for auto- vs allo-transplant Relapse: 17%	[57]
Kyriakou *et al.* (2009)	AILD	Chemosensitive: 27 Chemorefractory: 18	45	MAC: 25 RIC: 20	Siblings: 26	CSA + MTX/MMF	NRM: 25%	PFS: 53% (at 3 years) OS: 64% (at 3 years) RR: 20% (at 3 years) lower with GVHD	[55]
Jacobson *et al.* (2011)	PTCL/CTCL Nodal vs extranodal	NR	52	NR	NR	NR	Ac GVHD: 21% Ext ch GVHD: 27% (at 2 years) NRM: 27%	PFS: 30% (at 3 years) OS: 41% (at 3 years)	[56]

Ac: Acute; AILD: Angioimmunoblastic lymphadenopathy; ASCT: Autologous stem cell transplantation; BM: Bone marrow; Ch: Chronic; CR: Complete remission; CSA: Cyclosporine; CTCL: Cutaneous T-cell lymphoma; DLI: Donor lymphocyte infusion; Ext: Extensive; Flu: Fludarabine; *f/u*: Follow-up; GVHD: Graft-versus-host disease; HLA: Human leukocyte antigen; MAC: Myeoablative conditioning; MMF: Mycophenolate mofetil; MR: Matched related; MRD: Matched related donor; MTX: Methotrexate; MUD: Matched unrelated donor; NHL: Non-Hodgkin's lymphoma; NK: Natural killer; NR: Not reported; NRM: Non-relapse mortality; OS: Overall survival; PB: Peripheral blood; PBSC: Peripheral blood stem cells; PD: Progressive disease; PFS: Progression free survival; PR: Partial remission; PTCL: Peripheral T-cell lymphoma; pts: Patients; RIC: Redcued intensity conditioning; RR: Relapse rate; Sir: Sirolimus; Tac: Tacrolimus; TBI: Total body irradiation; TRM: Transplant-related mortality.

■ Outcomes after allogeneic transplants for PTCL

Most published studies have reported similar numbers at 3–5 years of follow up, with OS between 50 and 70% and PFS of up to 60%. Most have noted a plateau in relapse incidence noted within the first 2 years. Chemosensitive disease at the time of transplant seems to result in better outcomes in both OS and PFS [47,51,54,55] indicating that achieving disease control before allogeneic transplant is crucial to outcome. In one of the larger studies on 52 PTCL patients, Dodero *et al.* report superior 5-year relapse for patients allografted in CR compared with PR (24 vs 54%) and for those with chemosensitive disease compared with refractory disease (40 vs 77%) [51]. From City of Hope, the 5-year OS for patients in CR/PR compared with active disease was 72.9 versus 43.2% [53]. This series from Memorial Sloan Kettering also looked at pretransplant K_i-67 immunohistochemistry as a biological marker in PTCL and found that K_i-67 nuclear expression in ≤25% cells, indicating a more indolent histology, correlates with better OS [52]. Differences in OS and PFS for various histologies are reported for the 115 patients in the study by Le Gouill *et al.* as mentioned above [47]. The COH series [53,54] compared CTCL and PTCL histologies in their series and found similar outcomes for allogenic transplants in the two groups. The European Group for Blood and Marrow Transplantation Registry has reported outcomes only for AITL with a 3-year OS of 64% and PFS of 53%, similar to that seen in other studies [55]. In contrast, Jacobsen *et al.* report no difference in outcomes when histologies were stratified as nodal versus extranodal [56]. The series from Japan focuses on NK/TCL, based on the high prevalence in Japan, and report inferior 2-year OS and PFS of 30–40% compared with 70% for PTCL from the same registry. Nonetheless, patients undergoing either autologous or allogeneic hematopoietic cell transplantation

(HCT) for NK/TCL show better outcomes than those without HCT [57,58].

Very aggressive variants of PTCL, including the HTLVI associated ATLL, extra nasal NK/TCLs, T-PLL, HSTCL and the primary cutaneous γ/δ TCL. These diseases have been shown to have a very aggressive clinical course due to inherent chemoresistance and there are multiple failures with primary therapy. Hence high-dose therapy and ASCT approaches have generally not produced any long-term remissions in these patients (case reports, small series). Long-term remissions and improved survival has been reported in patients undergoing an allogeneic transplant in first remission [10].

■ TRM after allogeneic transplants

TRM after allogeneic transplant for PTCL has been reported to be as high as 30%, likely due to advanced stage disease and poor performance status in these patients. There is an increasing trend to use RIC particularly in the last 5 years due to the high TRM reported in earlier studies. This has resulted in lower TRM rates. Goldberg *et al.* reported the use of T-cell depletion in 47 patients, which may have contributed to the 25% incidence of chronic GVHD (compared with 60% and above in other series) and TRM of 18% at 45 months [52]. The incidence of acute and chronic GVHD is similar to transplants performed for other diseases and do not appear to be different based on the underlying disease.

■ Cord blood & haploidentical transplants

Currently there is very little data regarding the use of cord blood and haploidentical donors for the treatment of PTCL. However, there is a growing experience with these in the treatment of lymphomas including PTCL but the numbers remain small to distinguish specific features that may pertain to PTCL. Johns Hopkins has reported on 44 patients with PTCL who underwent related donor transplants that included 18 patients who received a haploidentical transplant [59]. The median age of this group was 60 years. The 2-year OS was 43% and PFS was 43%. Estimated 1-year non-relapsed mortality was reported as 11% for this group. They concluded that the outcomes were similar to the sibling transplants.

■ Conclusion regarding allogeneic transplantation in PTCL

The use of allogeneic stem cell transplant at least in some of the common nodal histologies of PTCL can provide long-term disease control for patients with chemo-sensitive disease, with most relapses occurring within the first 2 years. The risk of acute and chronic GVHD remains high but TRM can be reduced by using RIC to minimize regimen-related toxicities while maintaining the graft-versus-lymphoma effect. Disease relapses after an allogeneic transplant have been treated with DLI and there may be a correlation of GVHD with disease control. However chemosensitive disease and optimal disease control is needed for the best outcomes with this modality. For the most aggressive histologies, an allogeneic transplant can provide disease control but the numbers remain small and the experience is still limited. Most physicians still use fully ablative conditioning if possible in these situations to provide the best option for disease control particularly in young patients. Since most relapses occur within the first 2 years after transplant, consideration should be given to maintenance therapies using the newer targeted agents to reduce any residual disease and improve the outcomes after allogeneic transplant.

Conclusion & future perspective

The role of stem cell transplantation in PTCL continues to evolve. Questions remain as to which type of transplant to offer patients with PTCL either in the upfront or relapsed setting. A recent publication has looked at the outcome of 241 patients undergoing stem cell transplant for PTCL in the CIBMTR data base [60]. This report included all transplants including allogeneic and autologous transplants. They reported a 3-year PFS and OS of auto-HCT recipients beyond CR1 as 42 and 53%, respectively, which was not statistically significant from all transplants at 31% PFS at 3 years but the overall mortality was 3.5-fold higher with allogeneic approaches. Chemosensitivity and two or fewer lines of pretransplant therapy were prognostic for improved survival indicating the need to improve upfront therapies in these diseases. As we better define upfront and salvage therapies utilizing targeted T-cell-directed treatments, it will inevitably lead to improved transplant and overall patient outcomes. The next step is to incorporate these new targeted therapies into the treatment of salvage and conditioning-regimen patients who will truly benefit from a transplant and incorporate T-cell-directed agents into conditioning regimens.

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Executive summary

- Peripheral T-cell lymphomas (PTCL) carry worse outcomes than B-cell lymphomas.
- Stem cell transplant therapy is feasible for PTCL.
- Autologous stem cell transplantation performed during first remissions can improve disease free survival and possibly overall survival in PTCL.
- Autologous stem cell transplantation can salvage relapsed PTCL patients if they have chemosensitive disease.
- Allogeneic stem cell transplants can provide long term disease control for patients with relapsed PTCL through graft vs lymphoma effect.
- Rates of graft vs host disease and other treatment-related complications are not increased for patients with PTCL undergoing allogeneic stem cell transplants.
- Many patients with PTCL are either ineligible for transplant or have poorly controlled refractory disease thus making them transplant ineligible.
- Novel targeted therapies for PTCL are providing bridging therapy for many patients with relapsed disease allowing them to proceed with transplant.

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