Should Eligible Patients with T-Cell Lymphoma Receive High-Dose Therapy and Autologous Stem Cell Transplant in the Upfront Setting?

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Abstract Peripheral T-cell lymphomas (PTCL) are rare and aggressive subtypes of non-Hodgkin's lymphoma. Compared to B cell lymphomas, the immunologic phenotype of PTCL portends a poorer prognosis, with the exception of anaplastic large cell lymphoma bearing the anaplastic lymphoma kinase protein. Patients with PTCL tend to present clinically in advanced disease states, show lower response rates to chemotherapy, and suffer from more frequent relapses and shorter remissions. The rarity of these lymphomas has made it difficult to carry out prospective, randomized trials delineating optimal treatments. Conventional and intensified chemotherapy have led to reasonable responses, but in many studies, frequent relapses. Consequently, high-dose chemotherapy and autologous stem cell transplantation (ASCT) have been actively studied in both the relapsed and upfront setting. In addition, the impact of disease status at transplantation is being investigated, though the optimal disease state at transplant is still a matter of debate, as is the timing of transplant. This article seeks to review the literature on the role of ASCT in PTCL, as well as to clarify what may be the optimal disease state in which to offer patients with PTCL autologous transplantation, if at all.

Keywords Peripheral T-cell lymphoma · Non-Hodgkin's lymphoma · Autologous stem cell transplantation · Aggressive lymphoma · Upfront setting · Complete remission · High-dose therapy

Introduction

Peripheral T-cell lymphomas (PTCLs) are an uncommon subtype of non-Hodgkin's lymphoma (NHL), consisting of a variety of rare entities. PTCLs comprise approximately 10% of aggressive NHL in the United States and Europe [1–3, 4•]. Though there are multiple subtypes of mature T-cell and NK-cell neoplasms described in the 2008 World Health Organization classification, the three most commonly occurring subtypes of PTCL are PTCL not otherwise specified (PTCL-NOS); angioimmunoblastic T-cell lymphoma (AITCL), and anaplastic large cell lymphoma, further characterized by the presence or absence of the anaplastic lymphoma kinase (ALK) protein (CD30). These account for over 50% of all new diagnoses [5].

With the exception of ALK+ ALCL, which has a superior outcome compared to PTCL-NOS and ALK– ALCL, PTCLs are characterized by a more aggressive clinical course in contrast to their B-cell phenotypic counterparts, and are more likely to present in later stages, with extranodal disease, and B symptoms. In addition, they are associated with inferior overall survival (OS) and event-free survival (EFS) [4•, 6, 7]. This may be due to an independent negative prognostic impact of the T-cell immunophenotype, as well as a more unfavorable distribution of prognostic factors [8]. Beyond the T-cell phenotype and prognostic schemas such as the International Prognostic Index (IPI) and Prognostic Index for T-cell Lymphoma (PIT) [9, 10], few other prognostic markers exist. Although recently, molecular characterization of TCLs was undertaken with gene expression profiling. High expression of two immunosuppressive signatures was found to be associated with poor survival [11].

Standards of care or an optimal approach for most PTCL remain to be defined. Current conventional

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chemotherapy results in poor complete response (CR) rates and OS rates. High-dose chemotherapy (HDT) and autologous stem cell transplant (ASCT) have been studied in relapsed disease; however, there is insufficient evidence in the form of large, prospective randomized controlled trials to precisely define the role of HDT and ASCT in the first-line setting. The role of allogeneic stem cell transplant is also unclear.

Treatment: Chemotherapy Alone in PTCL

Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has informally been established as a standard treatment for PTCL, modeled after treatment for aggressive B-cell lymphoma. However, CHOP has never been prospectively compared to other regimens for people with PTCL. Response rates with CHOP or CHOP-like regimens have been reasonable, though durability of responses disappointing, thus prompting the theory that perhaps more intensive treatments are superior. Escalon et al. [12], at M. D. Anderson Cancer Center (MDACC), retrospectively evaluated CHOP along with other more intensive regimens such as HyperCVAD, ASHOP, MBACOS, MINE, and HCVID-Doxil in 135 patients with PTCL. The specific regimen was chosen by the treating physician but roughly followed eras of treatment. They found no significant difference in OS between patients treated with CHOP or other more intensive therapies (56% vs 62%, respectively). This held true even when patients with ALK+ ALCL were excluded.

The Groupe d'Etude des Lymphomes de l'Adulte (GELA) LNH-84 study evaluated the effects of intensification of chemotherapy in 737 patients with advanced-stage NHL, and later performed a subset analysis of 361 patients with available immunophenotyping (30% of whom had TCL). All patients received induction with three to four cycles of ACVB (Adriamycin, cyclophosphamide, vindesine, bleomycin, and methylprednisolone) with intrathecal (IT) methotrexate, followed by consolidation chemotherapy with high-dose methotrexate, ifosfamide plus etoposide, cytarabine, and L-asparaginase. They were then randomized to either intensification with two more cycles of consolidation chemotherapy, or observation. Approximately 72% of the entire group had a CR (71% B cell, 72% T cell) to this dose-intense regimen, although relapse rates were higher for patients with TCL compared to BCL (43% vs 23%, at 30 months though NS). The authors found that additional late intensification had no value in increasing survival or decreasing relapse rates compared to the baseline program [13].

Retrospectively, anthracyclines seem to contribute little to outcomes of people with PTCL. The International

T-cell Lymphoma Project found that the majority of patients with PTCL or NKTCL (other than ALK+ ALCL) did not clearly benefit from the use of an anthracycline-containing regimen over a non-anthracycline-containing regimen in terms of OS/PFS. Complete response rates to anthracycline-containing regimens such as CHOP have been moderate, ranging between 39% and 70% [4•]. A meta-analysis of 2912 patients (excluding ALCL) from a heterogeneous dataset retrospectively evaluated the role of anthracycline-based regimens as first-line treatment for PTCL. The estimated CR rate for anthracycline-based regimens among non-ALCL PTCL patients was 54.5%. The estimated 5-year OS for non-ALCL PTCL was 37.3% [14]. Gemcitabine-based regimens are also being explored. Gemcitabine has demonstrated good single-agent activity for cutaneous T-cell lymphoma in the relapsed setting, with a 75% ORR (22% CR, 53% PR) [15]. In addition, a study of 29 patients with heavily pretreated PTCL showed that gemcitabine had an ORR of 51% (CR 23%) [16]. Gemcitabine as part of combination chemotherapy also has revealed promising activity in small series. Sixteen patients with relapsed or refractory disease received gemcitabine, cisplatin, and methylprednisolone, with an ORR of 69% (19% CR, 50% PR) [17]. In the front-line setting, gemcitabine was studied in combination with etoposide and CHOP in 26 patients with newly diagnosed PTCL. The ORR was 77% (CR 61.5%, PR 15.4%), and median OS had not yet been reached, with a median follow-up of 383 days; encouraging results but not clearly better than CHOP alone. Based on these data, gemcitabine may be a feasible agent with the potential to impact on ORR in the first-line setting and is being actively investigated as a component of novel regimens for PTCL [18].

Though overall PTCL often initially responds favorably to chemotherapy, relapse rates remain unacceptably high, prompting the investigation of consolidative strategies to possibly improve outcomes.

ASCT in PTCL

Using the peripheral T-cell lymphoma prognostic index, 5-year OS ranges between 18% and 62%, depending on the prognostic factors involved. These outcomes are worse than those seen with diffuse large B-cell lymphoma (DLBCL), whose 5-year OS based on the IPI ranges between 26% and 73% [10]. Based on favorable results utilizing HDT and ASCT in relapsed and refractory high-grade B-cell lymphomas, clinicians have been prompted to evaluate the role of intensifying treatment with HDT and ASCT for PTCL in various contexts, given poor long-term responses to standard-dose chemotherapy [19].

HDT/ASCT as Salvage Treatment for PTCL: Retrospective Studies

Few prospective studies investigating the role of HDT/ASCT in T-cell lymphoma exist; however, several retrospective studies have addressed the issue in the relapsed and upfront setting (Table 1). They demonstrate 3 to 5 year survival rates following stem cell transplantation between 35% and 65%, approximating results observed with B-cell lymphomas. This wide range of outcomes, however, may in part reflect diversity of patient selection, with many studies including patients with the more favorable ALK+ ALCL. In addition, retrospective studies generally only report data on patients able to get to HDT/ASCT. With that significant caveat, most studies, despite heterogeneous conditioning regimens utilized, showed that in relapsed and heavily pretreated patients, high-dose therapy and hematopoietic stem cell rescue may be able to overcome the negative prognostic impact of the T-cell phenotype in a minority of patients.

Rodriguez et al. [20] from MDACC retrospectively evaluated 36 patients with relapsed or refractory PTCL treated between 1989 and 1998. Patients were heavily pretreated, with a median of three prior therapies. Seven patients with ALK+ ALCL were included. Twenty-nine patients received ASCT (80%) and seven received allogeneic transplants (19%). As seen in other studies,

induction regimens were varied. Eleven of 29 patients (38%) entered ASCT in CR. Following ASCT, 79% of patients (23/29) achieved CR. Comparisons between ASCT and allogeneic transplant yielded poor 3-year OS of 39% and 29%, respectively. Median PFS for ASCT was 32%, versus 14% for allogeneic transplant. In this study in heavily pretreated patients with PTCL, durable benefit following ASCT was limited to less than a third of transplanted patients.

Song et al. [21] reviewed 36 patients with relapsed or refractory TCL who underwent ASCT, and matched them to patients with aggressive B-cell lymphoma treated at the same institution undergoing ASCT. Patients were similar with respect to age, stage at relapse, presence of extranodal disease, and chemosensitivity to salvage treatment. All patients received high-dose melphalan and etoposide with or without total body irradiation, followed by ASCT. Seven patients with ALCL (ALK status unknown) were included. Three-year actuarial OS for patients with PTCL was 48%, and 3-year EFS was 37%. Compared to DLBCL, the 3-year EFS of patients with the PTCL NOS subtype was significantly inferior at 23% compared to 42% ($P=0.02$), though OS was not ($P=0.11$). As expected, patients with ALCL had better outcomes; 3-year EFS and OS were 67% and 78%, respectively. Patients with PTCL NOS fared worse when compared with ALCL (3-year EFS 23% vs 67%). This study showed inferior outcomes following

Table 1 Retrospective studies evaluating ASCT in peripheral T-cell lymphoma

Retrospective studies					
Study	Patients, <i>n</i>	DFS/EFS/PFS	OS	Included ALCL?	Other notes
Relapsed, refractory setting					
Rodriguez et al. [20]	36	Median PFS 32%	39% at 3 y	ALK+ <i>n</i> =7	Allogeneic <i>n</i> =7 ASCT <i>n</i> =29
Song et al. [21]	36	EFS 37% at 3 y	48% at 3 y	ALCL (unknown status) <i>n</i> =7	Patients compared to matched cohort of BCL
Kewalramani et al. [22]	24	PFS 24% at 5 y	33% at 5 y	ALK - ALCL	Patients compared to cohort of relapsed DLBCL
First-line setting					
Blystad et al. [25]	40	EFS 48% at 3 y	58% at 3 y	ALCL <i>n</i> =14	No difference in outcome for disease status prior to ASCT
Rodriguez et al. [26]	115	DFS 60% at 5 y	56% at 5 y	ALCL <i>n</i> =8	Superior OS for CR1 vs CR2: 80% at 5 y vs 50% at 5 y
Jantunen et al. [27]	37	NA	54% at 5 y	ALCL <i>n</i> =14	Trend toward superior OS for CR1 vs later: 63% at 5 y vs 45%
Rodriguez et al. [28]	74	PFS 63% at 5 y	68% at 5 y	ALCL <i>n</i> =23	All patients transplanted in CR1
Feyler et al. [29]	82	PFS 50% at 3 y	53% at 3 y	ALCL <i>n</i> =25	2-y OS for patients in CR1 64%, 2-y PFS 61%
Yang et al. [30]	64	PFS 44% at 3 y	53% at 3 y	NA	3-y OS for ASCT in CR1/PR1 60% vs salvage 38%

ALK anaplastic lymphoma kinase; ASCT autologous stem cell transplantation; DFS disease-free survival; DLBCL diffuse large B-cell lymphoma; EFS event-free survival; NA not available; OS overall survival; PFS progression-free survival

ASCT in patients with PTCL NOS compared with ALCL and DLBCL.

Kewalramani et al. [22] evaluated 24 patients undergoing ASCT with relapsed or refractory PTCL who responded to first-line or second-line chemotherapy and compared them with 86 consecutive patients with chemosensitive relapsed or primary refractory DLBCL. Patients with ALK+ ALCL were excluded, as were patients in whom ALK expression could not be documented. Five-year PFS rates for PTCL and DLBCL were 24% and 34%, respectively ($P=0.14$); the corresponding OS rates were 33% and 39%, respectively. No significant differences were found between the two groups with respect to time to disease progression or survival after progression. However, when the authors attempted to assess their dataset by evaluating patients at the time of relapse only rather than those undergoing ASCT, 83% of patients had relapsed, with a median PFS of 6 months from last salvage treatment. Twenty-eight percent of patients (70%) relapsed within 1 year [23].

A study by Smith et al. [24] from the Cleveland Clinic may more accurately reflect the true natural history of patients with relapsed and refractory PTCL undergoing ASCT for salvage. This single-center retrospective study evaluated patients with PTCL who underwent ASCT for relapsed and refractory disease over a 10-year period. All patients received a uniform chemotherapy-only high-dose regimen. Their 5-year OS and relapse-free survivals (RFS) were lower than what has been published in other studies: 34% and 18%, respectively.

In summary, these retrospective studies on HDT and ASCT for patients with relapsed or refractory PTCL demonstrate that patients with chemotherapy-sensitive disease may respond favorably to ASCT. When critically evaluating these studies, it is important to consider that most of them contain some type of bias, largely due to patient selection and inclusion of patients with more favorable PTCL subtypes, and in addition most include patients who went on to receive HDT/ASCT. While outcomes of patients transplanted for relapsed disease seem comparable to those of patients with relapsed B-cell lymphoma (with better outcomes suggested in patients able to achieve CR prior to ASCT), these results must be analyzed and interpreted carefully. Cautious application of the data is warranted, since as discussed below, many retrospective studies have better results than those demonstrated in prospective series of patients.

Retrospective Studies on HDT/ASCT as First-Line Treatment of PTCL

A few of the retrospective studies investigating the role of ASCT in relapsed or refractory PTCL also evaluated the

importance of first remission (CR1). A study by Blystad et al. [25] evaluated 40 patients with PTCL in first remission or at relapse. Fourteen patients (34%) with ALCL (ALK status unknown) were included. All patients received anthracycline-containing regimens prior to transplant. At the time of ASCT, 17 patients were in first PR or CR, and 23 were in second CR or PR. Preparative regimens were varied. The estimated 3-year OS among all patients was 58%; 3-year EFS was 48%. Median OS of patients with ALCL was 79%, compared with 44% for non-ALCL. Univariate analysis did not reveal significant differences in OS, RFS, or EFS with respect to disease status at transplantation. Three-year OS among all patients was slightly higher than that seen in other studies, likely reflecting the contribution from patients with ALCL. While univariate analysis did not reveal significant differences in OS, RFS, or EFS with respect to disease status at transplantation, patient groups were very small.

In contrast to the findings by Blystad et al., the Gel-Tamo group reported a survival benefit for patients receiving ASCT in CR1 [26]. In this study, 115 patients with PTCL underwent HDT and ASCT. Seven percent of patients had ALCL (ALK status unknown). Conditioning regimens consisted of both chemotherapy and chemoradiotherapy. Two thirds of patients had two or three risk factors according to the IPI, and 32% of patients ($n=37$) were transplanted in first CR. Among the entire group, 5-year OS was 56%, and DFS was 60%. Patients transplanted in CR1 had a survival benefit; at 5 years, OS was 80%, with DFS 79%, compared to those in second or more CR who had 5-year OS of 50% ($P=0.007$). Similar results were found for DFS at 5 years in patients transplanted in CR1 versus second or greater CR; 79% compared to 42% ($P=0.002$). Patient selection may have contributed to these favorable outcomes; the median age for patients in CR1 was 31 years. In stark contrast, OS, TTF, and DFS for refractory patients at transplant were 0%, supporting a limited, or lack of benefit from this therapeutic modality. These results suggest a benefit to ASCT in CR1, though these data must be interpreted cautiously, given the very young median age of patients, and the inclusion of those with ALCL.

A Finnish study conducted by Jantunen et al. [27] assessed 37 patients with PTCL of multiple subtypes (38% of whom had ALCL), who received HDT and ASCT over an 11-year period at various Finnish transplant centers. Sixty-five percent of patients had stage III or IV disease. Conditioning regimens were more uniform, consisting of either BEAM or BEAC. Disease status at time of ASCT was CR1 or PR1 in 18 patients (48%), and CR2 or PR2 in 14 patients (38%). Patients transplanted in first remission showed a survival benefit, with 5-year OS of 63% compared to 45% for patients transplanted later in their course (though this did not reach statistical significance). The median time to relapse or progression was 8 months. A trend emerged toward superior PFS at 5 years for patients in CR1 (64% vs 28%) compared with those

transplanted later, though this was not statistically significant. The projected 5-year OS for the entire group was 54%, with significantly better outcomes in patients with ALCL compared to other subtypes (85% vs 35%, $P=0.007$), as suggested by others [22, 25]. An analysis of outcomes excluding patients with ALCL was not undertaken, thereby limiting the generalizability of these results.

Rodriguez et al. [28] evaluated 74 patients with advanced-stage PTCL who received HDT and ASCT in first CR, including 31% with ALCL (ALK status unknown). Patients received mostly CHOP or other anthracycline-based regimens, followed by BEAM or BEAC (91%). With a median follow-up of 67 months, 5-year OS was 68% and PFS was 63%. When analyzing patients with ALCL, 5-year OS was 84% versus 61% in patients with non-anaplastic PTCL subtypes ($P=0.05$). Similarly, PFS was superior in this group. In both univariate and multivariate analyses, patients with two factors or less according to the PIT system had a 74% 5-year OS compared to 31% for patients with more than two factors. This suggests that HDT/ASCT may not offer an advantage over conventional chemotherapy in patients belonging to this latter high-risk group. These results are possibly better than those seen with standard chemotherapy; however, best results were observed in lower-risk patients as well as those with ALCL, thereby making the data difficult to interpret.

Feyler et al. [29] published a study of 82 patients with PTCL identified through national transplant registries in the United Kingdom and Australia, of whom 64 received ASCT, and 18 received allogeneic transplant. This registry included ALCL, which comprised 31% of patients. ALK+ and ALK-status was confirmed in 18% of patients. Thirty-one patients (48%) receiving ASCT were consolidated in first remission, with varied conditioning regimens. OS and PFS at 3 years were 53% and 50%, respectively. The authors found that chemosensitivity was an important prognostic marker; responders had improved 3-year OS at 58% compared to 36% in non-responders, defined as patients having PD or SD. Here, patients in any CR or PR status (first or second) or with stable disease prior to ASCT were defined as having chemosensitive disease. Patients in CR1 experienced 2-year OS and PFS of 64% and 61%, similar to data reported by Jantunen et al. [27]. In comparison, in patients receiving ASCT as consolidation therapy for relapsed disease (defined as CR2/PR/SD, $n=20$), the 2-year OS and PFS were 49% each. The application of these results, however, is confounded by the inclusion of SD as a marker of chemosensitivity.

In a Korean study by Yang et al. [30], 64 patients, of whom 70% had stage III or IV disease, received HDT/ASCT for PTCL at 14 different institutions. Most patients received CHOP-based chemotherapy; mobilization regimens varied. Sixteen patients (25%) underwent HDT/ASCT while in CR1, and 12 received ASCT (18.8%) while in PR1 after primary chemotherapy. The 3-year OS and PFS rates for the entire

group were 53% and 44.3%, respectively. Frontline transplantation in CR1 had favorable prognostic impact on OS, as suggested by others [27, 29]. Three-year OS rates differed for patients receiving ASCT in CR1 or PR1 compared to those undergoing transplant in the salvage setting: 60% versus 37.7%. High-dose therapy/ASCT showed little benefit in patients with high a-IPI or PIT. In the high a-IPI group, 3-year OS and PFS were not reached, while for patients with high PIT, 3-year OS and PFS were 20% and 7.5%, respectively.

With regard to ASCT in first complete remission, retrospective studies suggest the possibility that ASCT in this setting may possibly benefit patients with PTCL. However, given the inherent limitations of retrospective studies such as patient selection and treatment heterogeneity, definitive conclusions cannot be made. At best, these are hypothesis generating, and well powered, randomized prospective studies are needed to definitively assess a benefit over standard-dose chemotherapy. It is important to question, if the best results in retrospective studies are seen in low-risk patients with favorable histologies and responsive disease, is HDT/ASCT improving the outcome for all, or a means of selecting the more favorable patients?

HDT/ASCT for PTCL in the First-Line Setting: Prospective Studies, Non-PTCL Restricted

Two prospective randomized studies (LNH-87 and LNH-93) of the GELA have evaluated the benefit of upfront ASCT in aggressive lymphoma, and included a subset of patients with PTCL [31, 32]. In the LNH-87 trial, authors utilized induction/consolidation chemotherapy versus HDT/ASCT. In the LNH-93 trial, induction/consolidation chemotherapy was compared to a shortened induction chemotherapy followed by HDT/ASCT. A matched control analysis of both trials (52 patients [16%] had TCL [16%]) was later published, and authors were unable to conclude that ASCT was superior to alternative therapies for patients who achieved a CR. This conclusion also applied to patients with TCL, who had no benefit overall of transplant. However, it must be kept in mind that the alternative therapies were more dose intense than standard regimens such as CHOP, and included a consolidation phase.

Prospective Studies, PTCL Restricted

Only five prospective, T-cell-specific trials evaluating HDT and ASCT in TCL have been published (Table 2). The largest prospective PTCL-restricted trial conducted to date has thus far been published in abstract form only. Here, the Nordic group evaluated the impact of a dose-intensified chemotherapy schedule consisting of six cycles of biweekly CHOEP,

Table 2 Prospective studies evaluating ASCT in peripheral T-cell lymphoma

Prospective studies: First-line setting				
Study	Patients, <i>n</i>	OS	CR status prior to ASCT	Other notes
d'Amore et al. [33••]	166	57% at 3 y	85% in CR/PR	–
Corradini et al. [34]	62	34% at 12 y	56% in CR	For patients in CR, 10-y EFS 47% compared to 11% for non-CR
Rodriguez et al. [35]	26	73% at 3 y	NA	OS for patients in CR 87%
Mercadal et al. [36]	41	39% at 4 y	39% in CR	Disease status prior to ASCT had no difference in outcome
Reimer et al. [37]	83	48% at 3 y	73% in CR	–

ASCT autologous stem cell transplantation; CR complete remission; EFS event-free survival; NA not available; OS overall survival; PR partial remission

followed by consolidation with BEAM/ASCT for patients in CR1 or PR1. A total of 166 patients were enrolled, excluding ALK+ ALCL, most of whom (81%) had advanced-stage disease. Out of 155 evaluable patients, 85% were in CR/Cru ($n=132$) or PR ($n=51$). Seventy percent of patients received ASCT; the remaining did not proceed due to disease progression, toxicity, or failure to mobilize. After a median follow up of 3 years and 9 months, OS at 3 and 5 years for the entire cohort was 57% and 50%, respectively, while PFS at 3 and 5 years was 48% and 43%, respectively [33••].

Corradini et al. [34] conducted two prospective phase 2 studies between January 1993 and December 2003. Sixty-two patients with PTCL (including ALK+ ALCL) were enrolled, 82% of whom had stage II to IV disease. Patients received either high-dose sequential chemotherapy ($n=32$), or MACOP-B/MAD (methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycin/mitoxantrone, cytarabine) chemotherapy ($n=30$), followed by ASCT. High-dose therapy consisted of two courses of APO (doxorubicin, vincristine, prednisone), followed by DHAP (cisplatin, cytarabine, dexamethasone), and high-dose cyclophosphamide and cisplatin followed by etoposide. In both trials, patients with bulky or residual disease 1 month post-ASCT received radiation therapy. Of the 62 treated patients, 56% were in CR prior to ASCT, 10 (16%) were in PR, and 15 (24%) had POD. Forty-six patients (74%) ultimately underwent ASCT; inability to receive a transplant was largely due to progressive disease. Of the patients not receiving ASCT, three were rescued with an allogeneic transplantation and became long-term survivors; the remaining patients underwent conventional salvage regimens, with poor outcomes. The study had a long median follow-up of 6.3 years. On univariate analysis, ALK+ patients had an OS of 62% at 10 years versus 21% for non-ALK+. Overall survival at 12 years for the entire cohort was 34%. Disease status prior to ASCT also had prognostic significance, with CR having significant advantage over those not in CR. The 10-year EFS of patients in CR before ASCT was 47% compared to 11% not in CR, suggesting that

consolidation in CR with ASCT may offer a greater chance of long-term survival. Comparing histologic subgroups more closely, the authors discovered that patients with PTCL had estimated 12-year OS and EFS of 37% and 25%, respectively, which did not differ significantly from the whole group of non-ALK ALK+ patients.

A smaller study by Rodriguez et al. [35] evaluated 26 patients with high-risk PTCL. Patients received three cycles of MegaCHOP (cyclophosphamide 2 g/m², doxorubicin 90 mg/m², vincristine 1.4 mg, prednisone 60 mg/m²), and those who were gallium scan negative received another cycle of MegaCHOP followed by ASCT. Patients remaining gallium scan positive received two courses of IFE (ifosfamide and etoposide), and if PR or greater status was achieved, they went on to ASCT. Twenty-six percent of patients were unable to undergo ASCT secondary to progression of disease. Among all patients, OS and PFS at 3 years were 73% and 53%, respectively. However, of the 19 patients who were considered suitable to receive the transplant (having achieved a minimum of PR), corresponding OS, PFS, and DFS at 2 years from transplant were 84%, 56%, and 63%, respectively. The authors found no differences in outcome between patients with positive and negative gallium scans after three cycles of MegaCHOP, though there was a trend toward improved OS and EFS in those with negative scans. However, patients in CR or PR after MegaCHOP had superior OS at 3 years (83%) versus those with refractory disease.

The limitations of retrospective series are highlighted well here when evaluating data from Gel-Tamo's retrospective and prospective studies together. Their retrospective analysis in 2003 had a much larger patient sample ($n=115$), all of whom received ASCT though with induction regimens consisting of both chemotherapy and radiotherapy [26]. Overall, DFS and PFS were 56% and 60%, respectively, while patients in CR1 fared better with 5-year OS and DFS of 80% and 79%. Survival curves in this series appear to have plateaued after 20 months for patients in CR1 and after 50 months for patients in PR1. Conversely, in their prospective study, while

the medians are similar, the PFS curve demonstrates a continuous rate of relapse below 40% [35].

Mercadal and colleagues [36] reported different outcomes in 41 patients with PTCL who received intensive chemotherapy with high-dose CHOP (cyclophosphamide 2 g, doxorubicin 90 mg/m², vincristine 2 mg, prednisone 60 mg/m²) and three doses of ESHAP (etoposide, cisplatin, cytarabine, and prednisone). Modest responses were achieved to chemotherapy; 39% of patients achieved CR (four had Cru, and four had PR). In addition, a rather high number of patients (41%) experienced disease progression on chemotherapy. Out of 24 patients with CR, Cru, or PR who could have undergone ASCT, only 17 received that therapy. The achievement of CR after predicted for OS though no differences were found in terms of whether ASCT was carried out or not for the 24 patients in CR or PR. In this study the CR rate after intensive chemotherapy was lower than that seen in other studies [34], and patients had a high rate of treatment-related morbidity due to serious infections requiring hospitalization, possibly influenced by extent of disease in most patients (71% had stage IV). There was no apparent benefit to ASCT in this dataset as no significant differences were seen in OS and EFS for transplanted patients.

The largest published PTCL-specific prospective study evaluating front-line HDT/ASCT was conducted by Reimer et al. [37•]. Eighty-three patients with PTCL (excluding ALK+ ALCL) received four to six cycles of CHOP chemotherapy, and those achieving CR moved on to receive mobilization therapy with BEAM or etoposide, methylprednisolone, cytarabine, and cisplatin. Three quarters of patients had stage III or IV disease, and 51% had a high/high-intermediate risk a-IPI. Patients achieving less than CR after CHOP received two more cycles, and after a total of six, at least a PR was required for mobilization. Overall, RR to CHOP was 79%, and pre-transplant CR was achieved in 39%. Patients then proceeded to myeloablative radiochemotherapy with high-dose cyclophosphamide and TBI. Fifty-five patients (66%) received transplantation; the remainder did not, mostly due to POD. Twenty-two patients (40%) relapsed following HDT-ASCT, and in the intent-to-treat analysis the 3-year OS and PFS rates were 48% and 36%, respectively. These results reinforce similar outcomes reported in other smaller prospective studies evaluating upfront HDT-ASCT (Table 1). Not surprisingly, transplanted patients fared better than others, with an estimated 3-year OS of 71% for patients undergoing ASCT, versus 11% for those who did not.

Conclusions

HDT and ASCT are common treatment options for patients with PTCL. In the relapsed and refractory

setting, some series show comparable response rates and survival durations to those seen in patients with B-cell lymphomas for whom ASCT is a standard option, but others show very little durable benefit. Five prospective nonrandomized studies have evaluated the utility of upfront HDT/ASCT, with several survival rates at 3 years ranging between 39% and 73%. These results are comparable to those observed in retrospective studies, but longer follow-up is necessary to determine if a plateau is reached and cure rates possibly improved, as opposed to a delay in relapse. It appears that responding patients and perhaps those in CR receive the majority of the benefits. In Blystad's study [25], patients in CR1 had 5-year OS of 80%, compared to 50% for those in CR2 or beyond. Similarly, Jantunen et al. [27] found trends toward superior rates of PFS and OS at 5 years for patients in CR1 compared with those transplanted later: 64% versus 28%, and 63% versus 45%, respectively. Feyler's study [29] of 82 patients also found that patients in CR1 had better 2-year OS and PFS rates at 62% and 59%, respectively, compared to those in CR2, PR, or SD at the time of transplant. In that setting, survival rates dropped to 49%. However, interpreting retrospective series can be difficult given their inherent limitations and frequent inclusion of favorable histologies such as ALK+ ALCL. Many of the retrospective studies have survival curves that plateau, while most prospective studies show continuous rates of relapse, raising questions about inadvertent bias.

The aggregate of the studies reviewed here suggest that HDT/ASCT may yield better outcomes for responding patients, specifically those in CR1 following chemotherapy. Results of prospective studies on upfront ASCT also suggest that long-term survival can potentially be improved upon by using more aggressive treatment strategies so that a larger number of patients can reach CR, and therefore benefit more from ASCT. However, this treatment strategy may not be necessary for patients with ALK+ ALCL, who demonstrate superior outcomes compared to other subsets of PTCL. The lack of randomized studies precludes a definitive answer. But in patients with high-risk disease who have poor outcomes with chemotherapy alone, HDT/ASCT seems a reasonable option. The bulk of the retrospective phase 2 data shows the majority of transplanted patients are alive at their median follow-up. However, in the absence of randomized data, it will be difficult to conclude whether this approach truly improves PFS, favorably impacts on long-term survival, or merely selects for healthier, responding patients.

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