13 Autologous and Allogeneic Stem Cell Transplantation for T-Cell Lymphomas

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Introduction

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of diseases with variable histologies, immunophenotype features, geographic and ethnic frequencies, and clinical natural history [1]. At present, the standard treatment for PTCL is chemotherapy based on the CHOP regimen designed for the largest group of aggressive B-cell lymphomas. However, with the exception of ALK$^+$ ALCL the outcome is poor with low number of complete responses and early progression. These facts translate into a poor outcome with 5 year overall survival values of 25–35% and a subsequent pattern of early and continuous relapses [2].

Until very recently no specific drugs for T-cell lymphomas have been incorporated to the therapeutic armamentarium, and retrospective studies suggest that anthracyclines do not add benefit for these patients, so CHOP is still the most commonly used regimen. Intensification of treatment with high-dose therapy and autologous stem cell transplantation or a graft-versus-PTCL effect with allogeneic hematopoietic stem cell transplantation have been shown to be associated with prolonged disease-free survival in selected PTCL patients.

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Retrospective Studies of ASCT for PTCL

Autologous SCT is the standard procedure after salvage chemotherapy in relapsing and refractory aggressive B-cell lymphomas, provided that the tumor has proven chemosensitivity to the salvage regimen [3]. When this strategy is applied to PTCL, results are similar in these types of lymphomas to the corresponding larger group of aggressive B-cell lymphomas.

As shown in Table 13.1, the results for autologous stem cell transplantation in the salvage setting across a number of studies demonstrate an OS of 30–45% and a corresponding PFS of 25–35% at 3–5 years.

The transplant-related mortality (TRM) is generally low at 3–10% despite the fact that many of the patients are heavily pretreated. Benefit from autologous transplantation is most evident in patients who demonstrate chemosensitivity to the salvage regimen. In the largest series reported by the Spanish GELTAMO group, the results in 123 patients (25% of the patients with diagnosis of ALCL) demonstrate at 5 years a 45 and 34% of OS and PFS respectively. Only chemosensitive patients had benefit in terms of PFS [4].

Multivariate analysis revealed two prognostic adverse factors (adjusted-international prognostic

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Table 13.1 Main retrospective series on the use of ASCT in PTCL (Reprinted from Gutierrez et al. [45], with permission from Nature Publishing Group)

Study	Cases	% ALCL	Clinical setting	Survival	TRM (%)	Comment
Rodriguez [47]	29	NA	Salvage	3 year-OS: 36% 3 year-PFS: 28%	10	Results similar to DLCL
Blystad [48]	40	35	Frontline 1st CR Salvage	3 year-OS: 58% 3 year-PFS: 48%	7.5	Good results if chemosensitive
Song et al. [33]	36	55	Salvage	3 year-OS: 48% 3 year-PFS: 37%	17	Results similar to DLCL
Jantunen et al. [7]	19	38	Frontline 1st CR Salvage	5 year-OS: 45% 5 year-PFS: 28%	11	Better results in ALCL
Kewalramani [49]	24	0	Salvage	5 year-OS: 33% 5 year-PFS: 24%	NA	Results similar to DLCL
Smith [50]	32	65	Salvage	5 year-OS: 34% 5 year-DFS: 18%	3	Results worst than in DLCL
Feyler et al. [6]	33	31	Salvage	2 year-OS: 49% 2 year-PFS: 49%	3	Good results if chemosensitive
Rodriguez et al. [4, 5, 11]	74	31	Frontline 1st CR	5 year-OS: 68% 5 year-PFS: 63%	4	Very good results in 1st CR Worst if PIT > 2
Rodriguez et al. [4, 5, 11]	123	25	Salvage	5 year-OS: 45% 5 year-PFS: 34%	5	Results similar to DLCL Worst if a-IPI > 1 and B2M

ALCL anaplastic large cell lymphoma; *TRM* transplant-related mortality; *NA* nonavailable; *OS* overall survival; *PFS* progression-free survival; *DLCL* diffuse large-cell lymphoma; *CR* complete response; *PIT* prognostic index for peripheral T-cell lymphoma, : Elevated beta-2-microglobulin

index 2–3 and elevated beta-2 microglobulin) associated with favorable outcome in terms of PFS and OS. Using these and other covariates, a new prognostic index was defined for patients treated with ASCT in the salvage setting. As shown in Fig. 13.1, the value of this index relies on the identification of a subset of patients with the two adverse prognostic factors that, together with truly chemoresistant cases, do not benefit from ASCT consolidation and for whom other innovative therapies, including Allo-HSCT, should be tested.

The question as to the benefit of consolidation in first CR with transplant has benefit has been addressed in a number of prospective and retrospective studies. The largest prospective series by the GELTAMO group [5] describes the results of 74 patients who underwent ASCT consolidation after achieving a CR to induction chemotherapy regimen with CHOP or CHOP-like regimens.

With a prolonged follow-up of more than 60 months, the OS and PFS were 68 and 63%. In this study the only independent prognostic index able to identify a subset of patients who do not benefit from the ASCT as frontline consolidation at first CR was the presence of more than two adverse factors of the PIT (prognostic index for PTCL) index described by Gallamini and colleagues.

In another prospective study of 82 patients, 64 of them underwent ASCT with 50% of them in first CR. The OS and PFS at 2 years of these patients consolidated with ASCT in first CR were 62 and 59%, respectively supporting data of other series that show a substantial benefit of consolidation with ASCT in patients in first CR [6]. Similarly, another series from Finland reported 5-year OS and PFS of 63 and 64%, respectively. These results may be confounded by inclusion of ALK^+ patients, who have a more favorable outcome [7].

However, other studies are not so encouraging. The GELA performed a subset analysis of patients with PTCL included in the LNH93-3 aggressive lymphoma study [8]. Seventy-six patients with T-cell phenotype were analyzed in a randomized study of poor risk IPI patients comparing the GELA standard regimen ACVBP (doxorubicin, cyclophosphamide, epirubicin, vincristine, and prednisone) for

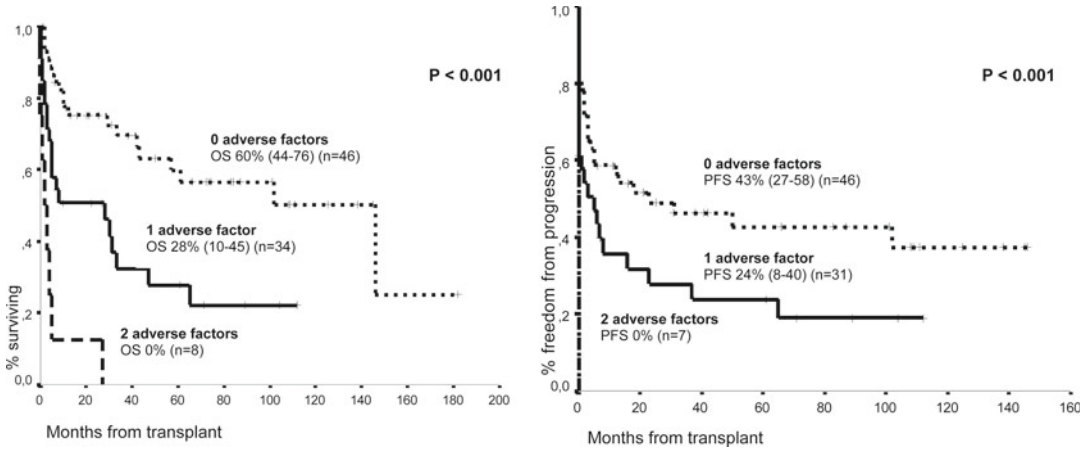

Fig. 13.1 Pretransplant value of a-IPI and beta-2-microglobulin for PTCL in the salvage setting; *OS* overall survival; *PFS* progression-free survival (Based on data from Rodríguez et al. [46])

four cycles and the experimental arm of CEOP/ECVBP (cyclophosphamide, epirubicin, vincristine, prednisone/epirubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) followed by consolidation with BEAM and ASCT. Results of this and pooled analysis of the prior LNH-87 study lead to the GELA investigators to state that consolidation with transplant did not add benefit to standard therapy even in CR patients.

In summary, review of these retrospective studies demonstrates several points. First ASCT is relatively safe with a low mortality. Second, most studies are based on BEAM or BEAM-like conditioning regimens with only a few studies using total body irradiation (TBI) in the conditioning regimen. Third, only chemosensitive patients are likely to benefit from the transplant.

Prospective Studies

At present, five prospective studies testing the hypothesis that consolidation with transplant in patients in remission after induction therapy have been reported (Table 13.2). The first study reported by Reimer et al. [9] describes the outcome of 83 patients with nodal aggressive histological subtypes: PTCL-NOS, AIL, and ALCL (ALK^-). The treatment plan consisted of four initial courses of CHOP with two additional cycles allowed if no CR was obtained. Only chemosensitive patients advanced to ASCT. The conditioning regimen was based on myeloablative radiochemotherapy (fractionated TBI and high-dose cyclophosphamide).

Of the initial 83 patients, 55 (66%) were able to undergo the transplant. At the time of transplant, 73% of the patients were in CR and 27% were in PR. After the transplant 87% of the patients achieved a CR. The results in an intent to treat analysis showed that 58% of the population obtained a CR and 8% a PR. With a median observation time of 33 months, the estimated 3-year OS, DFS, and PFS were 48, 53, and 36%, respectively. Of note that the 3-year OS of the patients who were transplanted was 71%.

Corradini et al. [10] reported the outcome of 62 patients transplanted at a median follow-up of 76 months. The 5-year OS and PFS were 54 and 40% respectively. As suggested by the authors, only patients with ALCL (ALK^+), patients with an age-adjusted international prognostic index of 0–1, or patients in first CR obtained benefit from the procedure.

The GELTAMO group [11] reported their prospective trial of 26 patients who were treated with three cycles of MegaCHOP (2 g/m^2 CY, 90 mg/m^2 Doxorubicin 1.4 mg/m^2, Vincristine 60 mg/m^2, Prednisone and mesna). After these three cycles, patients were evaluated with computerized tomography and gallium scan. At that point, the patients that were in CR received one or two more cycles of MegaCHOP and were transplanted. However those patients in less than CR received

Table 13.2 Prospective series on the use of frontline ASCT in high-risk PTCL (Reprinted from Gutierrez et al. [45], with permission from Nature Publishing Group)

	Corradini et al.	Reimer et al.	D'Amore et al.	Rodríguez et al.	Mercadal et al.
n	62 (19 ALK+)	83 No ALK+	121 No ALK+	26 No ALK+	41 No ALK+
Median age (years)	43	46	55	44	47
Regimen	(1) 2×APO > 2×DHAP > HD MTX/Mel (2) MACOP-B > HD AraC/Mito/Mel	4-6×CHOP + DexaBEAM > HD Cy + TBI	6×CHOEP-14 > BEAM	MegaCHOP/IFE > BEAM	3×MegaCHOP + 3×E-SHAP BEAM or BEAC
ASCT (%)	74	66	73	77	41
CR/PR pretransplant (%/%)	56/16	47/26	50/35	61/16	49/10
TRM (%)	4.8	3	4	0	3
OS (%)	34 (12 years)	48 (3 years)	67 (3 years)	75 (3 years)	39 (4 years)
PFS (%)	30 (12 years)	36	NA	53	30(4 years)
Follow-up (months)	76	33	24	24 postransplant	47
Risk status of patients	PTCL AA stage II–IV	PTCL AA stage II–IV Excluding ALK+	PTCL AA stage II–IV Excluding ALK+	PTCL a-IPI 2 or 3 a-IPI 1 & B2M Excluding ALK+	PTCL AA stage II–IV Excluding ALK+

ALK anaplastic lymphoma kinase; *APO* vincristine, doxorubicin, and prednisone; *DHAP* cisplatin, cytarabine, dexamethasone; *HD* MTX/Mel high-dose methotrexate and melphalan; *MACOP-B* methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone; *HD AraC/Mito/Mel* high-dose cytarabine, mitoxantrone, melphalan; *DexaBEAM* dexamethasone, BCNU, etoposide, cytarabine, melphalan; *HD Cy + TBI* high-dose cyclophosphamide plus total body irradiation; *CHOEP-14* cyclophosphamide, vincristine, doxorubicin, etoposide, and prednisone; *BEAM BCNU*, etoposide, cytarabine, melphalan; *MegaCHOP* cyclophosphamide, vincristine, doxorubicin, etoposide, and dexamethasone; *IFE* iphosphamide, etoposide; *E-SHAP* etoposide, cisplatin, cytarabine, prednisone; *BEAC BCNU* etoposide, cytarabine, cyclophosphamide; *CR* complete response; *PR* partial response; *TRM* transplant-related mortality; *OS* overall survival; *PFS* progression-free survival; *AA* Ann Arbor; *a-IPI* adjusted-international prognostic index; □ elevated; B2M beta-2-microglobulin

3 cycles of the salvage regimen Ifosfamide and Etoposide and if in at least PR went to the transplant. With this strategy the OS and PFS at 3 years were 72 and 53% respectively. Interestingly still 23% of the patients did not receive the transplant, mainly due to early progression. In addition, there was no difference in outcome in early responders compared to the group that received the salvage regimen after not being in CR with the initial induction regimen.

The largest prospective study was reported by the Nordic Lymphoma Group [12]. With a median of 3 years of follow-up, they reported approximately 60% of transplanted patients were still alive. In this study the induction regimen was a dose-dense regimen of CHOEP-14.

Another study reported by Mercadal et al. [13] from the GELCAB Spanish group included 41 patients who were treated with chemotherapy and then transplant if in remission. Only 17 out of 41 patients (41%) underwent the planned transplant due to progression and toxicity. Interestingly, only 23% of the patients transplanted in chemosensitive remission relapsed vs. 57% of those patients who were chemosensitive but non-transplanted for various reasons. Similarly the 4-year PFS was 59% for the patients transplanted vs. 29% for the chemosensitive non-transplanted group. This study confirms the earlier retrospective data that only patients in chemosensitive are likely to benefit from consolidation with the autologous stem cell transplantation.

Although these results are encouraging, approximately 20–30% of the patients do not get to transplant for early progression or toxicity and another 20–30% of those in CR after the transplant relapse of their disease. Thus better induction regimens with new drugs and therapeutic maneuvers to maintain the remission posttransplant should be the focus of the next clinical research efforts**.**

In summary the existing data suggests that patients who do not benefit from the ASCT in the salvage setting are those who are chemorefractory pretransplant and/or those with an age adjusted IPI ≥2 and an elevated beta-2 microglobulin. These patients need new approaches including allogeneic stem cell transplantation procedures or innovative experimental treatments.

In addition, retrospective data suggest that only patients in low-risk groups of the PIT system and in remission after induction therapy seem to obtain benefit from the ASCT consolidation. Randomized studies are needed to confirm that consolidation with ASCT improves the outcome of these patients.

Stem Cell Transplant in Angioimmunoblastic T-Cell Lymphoma

Angioimmunoblastic T-cell lymphomas are a subset of aggressive T-cell lymphomas in which the data suggests that there may be a benefit for autologous transplantation in first remission. A retrospective multicenter study of 146 AITL patients has been reported by the European Bone Marrow Transplant group (EBMT) [14]. At a median follow-up of 31 months, they reported a 59% overall survival and a relapse rate of 51%. Interestingly the non-relapse mortality was 7% at 24 months. Disease status at transplantation was identified as the major factor associated with the outcome. Patients transplanted in CR had a PFS of 56% at 48 months vs. 30 and 23% respectively for those chemosensitive and chemorefractory disease patients.

These data highlight once again, the fact, that basically patients in CR prior to the transplant are the ones who benefit the most. However, 25% of refractory patients also had benefit. Autologous transplantation could be considered in selected refractory patients, and early transplantation might represent the best option for patients in CR.

Other smaller series by the GELTAMO (Grupo español de linfomas y trasplante autologo de médula ósea) reported similar outcomes.

In this study [11], 19 patients underwent a transplant in first remission (15 cases) and in the salvage setting (4 cases). After the transplant, 79% achieved a CR and at 3 years the PFS and OS were 55 and 60%, respectively. In this study, patients who were transplanted in a refractory disease status did not benefit from this procedure.

Thus, with the small experience available and without the robustness of a randomized study, it

seems that consolidation with transplant in AITL patients chemosensitive prior to the transplant demonstrated benefit in both PFS and OS. However, longer follow-up and especially data from the ongoing randomized studies are needed to warrant this therapeutic modality as the new standard frontline therapy of these lymphomas.

Autologous Stem Cell Transplantation in Cutaneous Lymphomas

Patients with cutaneous T-cell lymphomas who have advanced disease with extensive nodal involvement, cutaneous tumors, or large cell transformation have a poor prognosis with an estimated median survival of 1–4 years. Current therapy based on systemic standard regimens for aggressive lymphomas yields usually responses that generally are short lived with a recurrent pattern of relapses. Therefore, intensification of treatment has been a logical step to take in these malignancies. However, there is a paucity of data concerning ASCT in these lymphomas. In fact, only case reports or small series with no more than ten patients have been reported. CTCL, subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous gamma–delta T-cell lymphomas, and CD30-cutaneous large T-cell lymphoma report responses to high-dose therapy that are short lived with short progression-free survival rates [15–17]. In this setting, the experience with allogeneic HSCT is much more promising [18]. Consolidation with autologous stem cell transplantation is not considered a standard of care in these patients.

Autologous Transplantation in Extranodal NK/T-Cell Lymphoma

Treatment outcomes for NK/T-cell lymphoma vary according to disease stage and location. Overall, long-term survival is reported as 30–40% for patients with upper aerodigestive nasal locations and significantly lower for patients with widespread disease [19]. Due to these unfavorable results with standard chemo-radiotherapy regimens, ASCT has been tested in both: as consolidation of first remission or in the salvage setting.

Although the experience with consolidation with ASCT is small, there may be a trend toward improved survival when compared with historical controls. In a multinational, multicenter, controlled trial, Lee et al. [20] reported a significantly higher disease-specific survival in the ASCT group in patients who were in complete remission at the time of the procedure, 87% for the ASCT group vs. 68% for the standard treatment group ($P = 0.02$). In contrast, the patients transplanted not in CR did not benefit from the procedure. Au et al. reported a similar finding in a series of 18 patients [21].

Thus, with the small experience available at present and without randomized studies to convince us the superiority of consolidation with ASCT, it seems that patients in first CR benefit from the procedure. For patients in refractory disease or in second remission in the salvage setting, the available results are generally poor; therefore, other options including allogeneic transplant procedures if feasible should be offered as would be discussed later in this chapter.

Prognostic Factors in the Transplant Setting

Several systems have been proposed for PTCL and NK/T-cell lymphoma. However the impact of these systems for patients treated with ASCT is not known. In one series, the PIT (prognostic index for PTCL) [22] as described by Gallamini et al., which system take into account, age, PS (ECOG, LDH, and bone marrow involvement as discrete covariates), predicted outcome in patients consolidated in first CR with ASCT better than the IPI [5]. In the salvage setting, the GELTAMO group proposed a new system based on two discrete variables: the IPI and the beta-2 microglobulin. In their series, patients who presented with both age-adjusted IPI higher than one and an elevated B2m had an inferior outcome with ASCT in the salvage setting. Clearly these patients need other therapeutic options including if feasible, allogeneic transplant [4].

Allogeneic Transplantation for PTCL and Cutaneous T-cell Lymphomas (CTCL)

Allogeneic stem cell transplantation (alloSCT) is an effective salvage treatment for some histotypes of relapsed non-Hodgkin lymphomas (NHL). Its peculiar efficacy is partly ascribed to the so-called *graft*-versus-*lymphoma* (GVL) *effect*, an immune mediated reaction operated by the transplanted immune system against the lymphoma cells. The existence of a GVL effect is mainly supported by three evidence: (1) tumor responses were observed after immune suppression withdrawal, (2) donor lymphocyte infusions (DLI) alone can cause tumor regression, (3) concomitant to the onset of acute graft-versus-host disease (GVHD) [23, 24] a lymphoma regression has been sometimes observed. Low grade NHLs have shown the most striking results, since alloSCT can provide a tumor-free graft and the indolent course of the disease allows the full exploitation of the GVL effect [25–27]. On the other hand, less data are available for aggressive histologies, and in particular for rare entities such as T-cell lymphomas [28–30].

In this chapter, the clinical results obtained in the most common subtypes of T-NHL, such as PTCL and primary CTCL, have been reported. In the largest prospective study published so far, 288 PTCL patients treated with different antracycline-containing regimens showed a 5-year overall survival (OS) and event-free survival (EFS) significantly worse compared with diffuse large B-cell lymphomas (DLBCL), with the exception of Alk-positive anaplastic T-cell lymphomas [31]. High-dose chemotherapy and autologous stem cell transplantation (autoSCT) in relapsed or newly diagnosed PTCL significantly changed the course of the disease in selected subsets of patients. Disease-free survival (DFS) and OS ranged between 35 and 45% respectively in most of the studies for relapsed patients [32, 33]. In a prospective study of high-dose chemotherapy as up-front therapy for PTCL, the outcome was improved only for patients with an age-adjusted international prognostic index (aaIPI) of 0–1, or in complete remission (CR) before transplantation or in case of Alk-positivity [10]. In general the main cause of treatment failure in autoSCT studies was disease progression before transplantation, suggesting that more intensive therapies and new drugs are needed to improve disease control [5, 10].

Similarly, in relapsed and advanced stage CTCL (Sezary syndrome (SS) and mycosis fungoides (MF)], there is no effective standard care and chemotherapy regimens usually induce transient responses that are not able to change the prognosis of these patients. The experience with autoSCT is very limited and not encouraging since most of the patients relapsed. The reinfusion of malignant cells with the graft and the failure of T-cell depletion procedures contributed to the poor results published so far [18]. The concept emerging from this brief introduction is that different mechanisms of tumor-killing are required to improve the outcome of Alk-negative PTCL and advanced CTCL.

Peripheral T-Cell Lymphomas

A retrospective analysis by Kim et al. on 233 relapsed lymphoma patients receiving a myeloablative alloSCT from a related or an unrelated donor showed a 2-year cumulative incidence of relapse of 21%, whereas the cumulative incidence of TRM was 40%. While they included a large number of aggressive lymphomas ($n=111$) in this study, there were 51 patients with PTCL. The 2-year OS for aggressive lymphomas was 42%, and patients with PTCL had a better survival than those affected by DLBCL, suggesting that T-cells can be a good target for donor-derived immune cells [34]. In this series, chemorefractory disease and a failed autoSCT were identified as adverse prognostic factors for both OS and TRM.

Le Gouill et al. have recently reported a retrospective review of allogeneic stem cell transplantation in 77 patients with PTCL (anaplastic large cell lymphoma (ALCL) ($n=27$), PTCL-unspecified ($n=27$), angioimmunoblastic T-cell lymphoma (AIL) ($n=11$), and rare subtypes ($n=12$)]. The majority of the patients (74%) received myeloablative conditioning and were allografted from HLA identical siblings (78%). This study included mainly patients with chemosensitive disease (70%). The results of this study were rather encouraging

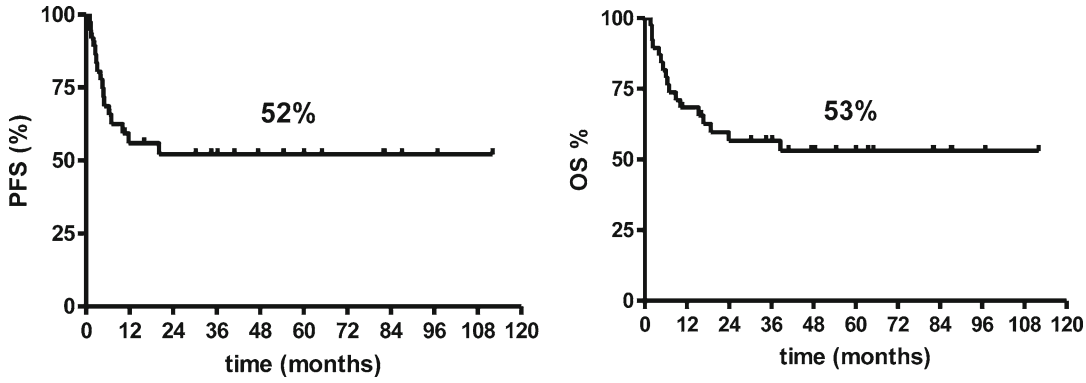

Fig. 13.2 Survival curves of relapsed patients affected by PTCL receiving RIC allogeneic stem cell transplantation; *PFS* progression-free survival; *OS* overall survival

with a 57 and 53% 5-year OS and EFS, respectively. In addition, they reported several interesting observations: (1) the OS was better in the nodal subtypes (55–80%) as compared to other histopathological subtypes (33%), (2) better OS and EFS were observed in patients receiving fewer prior therapies before alloSCT and/or with chemosensitive disease, (3) the authors observed an unexpected 5-year OS of 30 in patients with chemorefractory disease [35]. While survival was encouraging, but toxicity is still too high.

In order to decrease the toxicity and TRM of myeloablative alloSCT, reduced-intensity or non-myeloablative conditioning (RIC) regimens have been developed from the beginning of 1990s. Unlike myeloablative conditioning which relies mainly upon high-dose chemotherapy and/or radiotherapy to eradicate the malignant cells, RIC regimens based their activity more on the GVL effect. Most of the studies performed to date have shown that RIC regimens are associated with a reduced TRM; therefore, this strategy can be offered to the elderly or heavily pretreated patients or patients affected by comorbidities [36].

A small pilot study first showed that RIC alloSCT is feasible and effective in relapsed PTCLs [37]. After a thiotepa–fludarabine–cyclophosphamide based regimen 17 patients received HLA-identical allogeneic stem cells. The 2-year TRM was 6%, supporting the feasibility of this strategy. Fourteen of seventeen enrolled patients were alive (12 in complete remission) after a median follow-up of 28 months with an estimated 3-year OS and progression-free survival (PFS) of 81 and 64%, respectively. Notably 15 of 17 patients were chemosensitive at transplant, and this can also explain the good clinical results (Fig. 13.2).

A recent update of that pilot study including 38 patients confirmed the original observations. Patients were transplanted at relapse, after a median of two lines of therapy (range, 1–4) and 54% of them had failed a previous autoSCT. Thirty-five percent of the patients were in CR at transplant, whereas 40% were in partial remission (PR). The lymphoma subtypes were distributed as follows: unspecified PTCL $n=15$, ALCL $n=9$ (Alk-negative = 6, Alk-positive = 3), angioimmunoblastic $n=6$, intestinal $n=3$, others $n=5$. At a median follow-up of 50 months, 21 of 38 patients were alive ($n=19$ in CR, $n=2$ with disease), 12 died of disease, and 5 died of TRM (Fig. 13.1). The median time to relapse was 140 days (range, 38–603). In 34 of 38 evaluable patients the incidence of acute and chronic GVHD was 47 and 42%, respectively. The PFS was influenced by histotype and disease status before transplant. In fact, 3-year PFS was 75% for both angioimmunoblastic and unspecified PTCL and 40% for ALCL and the other subtypes. Patients in CR, PR, or chemorefractory at transplant experienced a 3-year PFS of 66, 52, and 25%, respectively. Eight patients received DLI with or without chemotherapy for relapsed or persistent disease: three patients achieved a long-lasting CR (median follow-up of 65 months (range, 84–64)), one patient achieved PR, and the others showed progressive disease [38].

A recent phase II prospective trial on 194 patients undergoing an RIC alloSCT has further supported our previous observation that alloSCT may overcome the unfavorable prognostic impact of T-cell phenotype. In fact, at a median follow-up of 5 years, PFS and OS were not significantly different between patients with relapsed aggressive lymphoma of B- or T-cell origin (PFS: 63 vs. 57% at 5 years, $p=0.45$; OS: 67 vs. 55% at 5 years, $p=0.51$) [39].

A recent retrospective analysis of the European Blood and Marrow Transplantation group has been conducted in 45 patients affected by AIL: 25 transplants were myeloablative and 20 were based on reduced-intensity conditioning. In this cohort of patients, mainly with chemosensitive disease, the cumulative incidence of relapse was limited (20% at 3 years). The 3-year OS and PFS were 64 and 54%, respectively, with a plateau in the survival curve after the first year from the transplant [40]. The intensity of conditioning regimen did not have a significant impact on NRM, relapse risk, and overall survival (Table 13.3).

Although these results are encouraging, the disease progression before transplantation remains an unresolved issue affecting approximately 30% of the patients at diagnosis. In the attempt to identify an active salvage regimen, alemtuzumab has been associated with chemotherapy. After eight courses of CHOP-Campath, 17 out of 24 patients achieved CR (71%), and 13 of them had a median duration of 11 months [41]. Wulf et al. demonstrated that alemtuzumab, associated or not to chemotherapy, was able to induce lymphoma remission before alloSCT in six of ten patients with advanced PTCL [42]. Although the follow-up was very short (only 7 months), six of these patients remained in remission after allografting.

Cutaneous T-Cell Lymphomas

The first experience of alloSCT in patients affected by CTCL was restricted to ten young patients receiving myeloablative conditioning regimens [18]. Four of ten patients relapsed after alloSCT, but responded to the withdrawal of immunosuppressive medication and/or donor lymphocytes infusions suggesting the existence of "graft-versus-CTCL effect."

CTCL typically affects the elderly (median age at diagnosis 60 years); therefore RIC regimens have been explored also in this setting. Molina et al. conducted a retrospective study, including eight patients heavily pretreated ($n=5$ SS, $n=3$ MF). Half of them received an RIC regimen consisting of fludarabine and melphalan, and four of eight were allografted from unrelated donors [43]. All the patients achieved a clinical remission, but two of them died of TRM. Interestingly, before alloSCT, six patients showed clonal T-cell receptor γ-chain gene rearrangements (TCRγ R) in peripheral blood or bone marrow, that resulted negative in the posttransplant PCR studies. Patients affected by MF with cytogenetic abnormalities usually have a very poor outcome. In this study, all the patients with such abnormalities achieved a cytogenetic remission.

Onida et al. reported the outcome of 15 patients with advanced CTCL ($n=9$ MF, $n=6$ SS), refractory to a median of three previous lines of treatment. At median follow-up of 41 months, the results were encouraging with an estimated 5-year PFS of 60% [44] (Table 13.4).

The optimal conditioning regimen and the better timing for alloSCT are currently unknown, but these preliminary results are interesting and should stimulate novel collaborative efforts for prospective trials.

In summary, RIC alloSCT (a) was able to decrease significantly TRM, thus elderly and/or heavily pretreated patients can become eligible for alloSCT; (b) can produce clinical results supporting the existence of a "graft-versus-T-cell lymphoma" effect; (c) an up-front strategy with RIC alloSCT can be considered in patients below 65 years of age in the context of controlled prospective trials.

The challenge still remains for the 30% of patients who progress despite any treatment at diagnosis, and for them we need novel agents to induce a remission state before any transplant procedure. For those responding and then relapsing, thus showing a story of chemosensitive disease, alloSCT might be a reasonable option up to 65 years of age.

In conclusion, with the available information concerning these two stem cell transplantation procedures, we propose a working treatment algorithm for PTCL excluding anaplastic large T-cell lymphomas ALK$^+$ cases that is depicted in Fig. 13.3.

Table 13.3 Allogeneic stem cell transplantation in relapsed PTCL

Author	No. Pts	Chemosensitive disease (%) before alloSCT	Type of conditioning regimen	NRM (%)	PFS (%)	OS (%)
Kim et al. [34]	58 PTCL-unspec. ($n=22$) Others ($n=36$)	–	Myeloablative (100%)	42[b] (2 years)	–	70 (2 years) PTCL-unspec. 30 (2 years) NK/T-cell
Corradini et al. [37]	17 PTCL-unspec. ($n=8$) Others ($n=9$)	10 (60%)	RIC (100%)	6 (1 year)	64 (3 years)	81 (3 years)
Corradini et al. [39][a]	28	22 (79%)	RIC (100%)	15[b] (1 year)	57 (5 years)	55 (5 years)
Le Gouill et al. [35]	77 PTCL-unspec. ($n=27$) ALCL ($n=27$) AITL ($n=11$) Others ($n=12$)	54 (70%)	Myeloablative (74%) RIC (26%)	34 (5 years)	53 (5 years)[c]	57 (5 years)
Kyriakou et al. [40]	45 All AITL	27 (60%)	Myeloablative (56%) RIC (44%)	25 (1 year)	54 (3 years)	64 (3 years)

Pts patients; *alloSCT* allogeneic stem cell transplantation; *NRM* non-relapse mortality; *PFS* progression-free survival; *OS* overall survival; *PTCL-unspec.* peripheral T-cell lymphomas unspecified; *ALCL* anaplastic large cell lymphoma; *AITL* angioimmunoblastic T-cell lymphomas; *RIC* reduced-intensity conditioning

[a]Abstract report

[b]The value was the NRM for all lymphomas not only PTCL

[c]The value reported is the event-free survival

Table 13.4 Allogeneic stem cell transplantation in relapsed CTCL

Authors	No. Pts	Chemosensitive disease before allo-SCT	Type of conditioning regimen	NRM (%)	PFS (%)	OS (%)
Molina et al. [43]	8 4 SS 4 MF	All refractory	Myeloablative (50%) RIC (50%)	25[b] (4 years)	–	75[b] (4 years)
Onida et al. [44]	15 6 SS 9 MF	All refractory	RIC (100 %)	20[b] (3 years)	60 (3 years)	–

Pts patients; *alloSCT* allogeneic stem cell transplantation; *NRM* non-relapse mortality; *PFS* progression-free survival; *OS* overall survival, SS Sezary Syndrome, MF Mycosis Fungoides, RIC reduced-intensity conditioning
[a]Abstract report
[b]The value was given as frequency

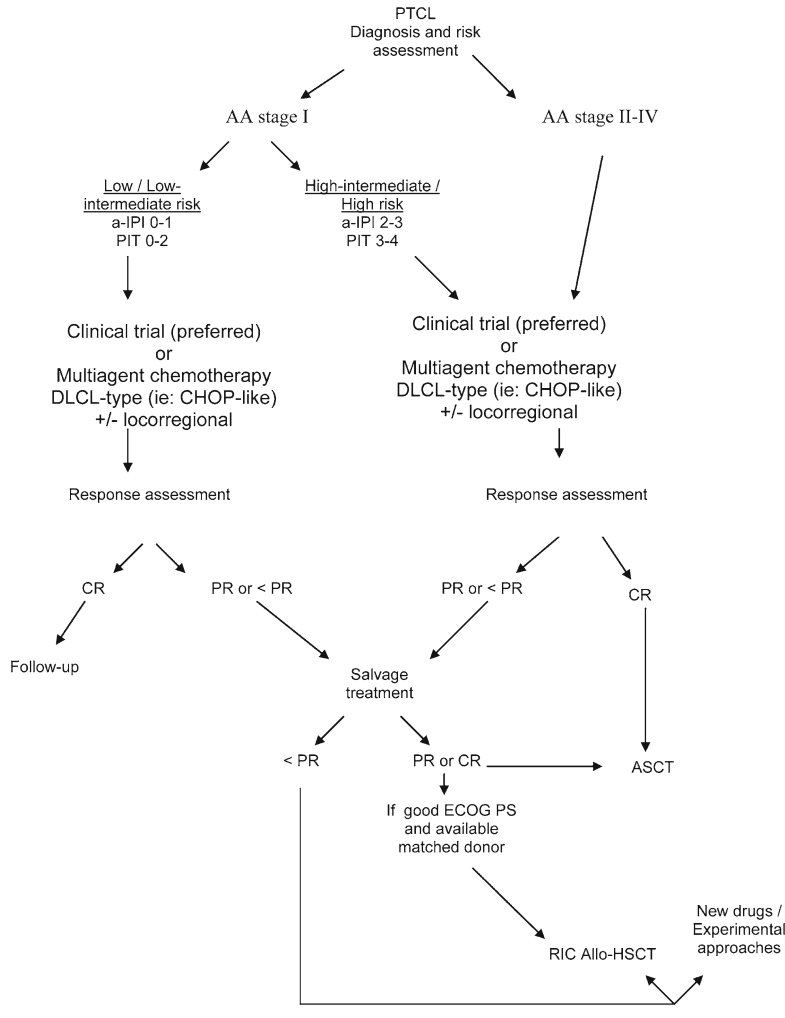

Fig. 13.3 Proposed treatment algorithm for PTCL (excluding ALK+cases). *PTCL* peripheral T-cell lymphoma; *AA* Ann Arbor; *a-IPI* adjusted International Prognostic Index; *PIT* prognostic index for peripheral T-cell lymphoma;, *DLCL* diffuse large-cell lymphoma; *CR* complete response; PR partial response; *ASCT* autologous stem cell transplantation; *ECOG* PS Eastern Cooperative Oncology Group Performance Status; *RIC* reduced-intensity conditioning; *Alo-HSCT* allogeneic hematopoietic stem cell transplantation

Since, these groups of lymphomas are currently a very active area of research, new upcoming information might modify this therapeutic proposal.

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