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Autotransplant in peripheral T-cell lymphomas

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Peripheral T/NK-cell lymphomas (PTCL) comprise a heterogeneous group of rare diseases accounting for approximately 10-15% of all non-Hodgkin's lymphomas. Most studies revealed the T-cell phenotype as a negative prognostic marker.¹⁻⁴ Due to their usually indolent course, primary cutaneous T/NK-cell lymphomas should be distinguished from the remaining PTCL and are not discussed here. A standard therapy for PTCL has not been defined, yet with the exception of the ALK-positive anaplastic large cell lymphoma (ALCL) that shows high overall survival rates after anthracyclin-based (CHOP-like) chemotherapy.⁵ For the remaining PTCL conventional chemotherapy leads to poorer results compared to aggressive B-cell lymphomas and sustaining complete remissions are achieved in only 15 to 42% of the patients.⁶⁻¹⁰ To overcome this therapeutic dilemma a more aggressive treatment strategy such as high-dose therapy with autologous stem cell transplantation (ASCT) seems a reasonable approach.

High-dose therapy and autotransplantation as first-line therapy in PTCL

So far, no prospective randomized PTCL-restricted studies are available to assess the impact of high-dose therapy on PTCL as up-front therapy. Two French trials by the GELA (*Groupe d'Etude des Lymphomes de l'Adulte*) investigated high-dose therapy in poor-risk, aggressive NHL, including PTCL.^{11, 12} The LNH87-2 study compared consolidative sequential chemotherapy with a high-dose chemotherapy regimen for patients exhibiting complete remission after anthracycline-containing induction therapy.¹¹ Only 16 of the 22 patients randomized to receive high-dose therapy received transplantation because of early progression. In an

intent-to-treat analysis, the authors did not find any difference between high-dose therapy and sequential consolidation in terms of overall survival (OS: 64% and 67%, respectively) or disease-free survival (DFS: 55% and 56%, respectively) after a 5-year follow-up.¹³

In the GELA trial LNH-93-3, patients were randomized between ACVBP (doxorubicine, cyclophosphamide, vindesine, bleomycin, prednisone) followed by sequential consolidation and a shortened induction treatment followed by consolidation with BEAM and autologous stem cell support.¹² In a subgroup analysis for the 76 patients with PTCL no significant difference in event-free survival (EFS) and OS could be detected between B-cell and T-cell lymphomas. However, the results might be biased by the inclusion of ALCL.

Recently the data of both trials were pooled and also matched-control analysis was performed.^{14, 15} The authors did not find a significant benefit for an upfront autotransplantation in PTCL. However, the limited number of patients (only 16 with non-ALCL/non-precursor T-cell lymphoma PTCL) in the high-dose group and the restriction to high-risk lymphoma do not allow to definitely assessing the impact of autotransplantation in this setting.

Two studies show data on high-dose therapy with ASCT restricted to patients with angioimmunoblastic T-cell lymphoma (AIL).^{16, 17} In 14 of the 29 patients in whom high-dose therapy was administered in first remission Schetelig *et al.* found a 5-year OS of 60% that did not significantly differ from the subgroup in which ASCT was performed as salvage therapy.¹⁶ Rodriguez *et al.* published data on 19 patients with AIL including four relapses who received mainly BEAM or BEAC as high-dose therapy. The 5-year OS was 60% after a median follow-up period of 25 months.¹⁷ Our own multicen-

Table 1. Studies on high-dose therapy and autotransplantation in PTCL as first-line therapy.

a) Retrospective					
Author (year)	n	Regimen	Response	OS	Comment
Schetelig (2003) ¹⁶	14	Diverse	86% CR	60% (5-year OS)	only ALL
Rodriguez (2005) ¹⁷	19	BEAM/BEAC	76% CR	60% (5-year OS)	Incl. ALCL
b) Prospective					
Author (year)	n	Regimen	Response	OS	Comment
Haioun (2000) ¹¹	18	Maintenance	No data	No data	Incl. ALCL and precursor T-cell lymphoma
	14	CBV			
Gisselbrecht (2002) ¹²	43	BEAM	No data	32% (5-year OS)	Incl. ALCL and precursor T-cell lymphoma ¹
	33	Maintenance		39% (5-year OS)	
Reimer (2005) ¹⁹	65	Cy/TBI	65% CR/PR	54% (2-year OS)	No ALK+ ALCL
D'Amore (2005) ²⁰	47	BEAM	70% CR/PR	57% CR after 17 mo	No ALK+ ALCL
Lopez-Guillermo (2005) ²¹	34	HighCHOP/ESHAP	58% CR/PR	38% (4-year OS)	No ALK+ ALCL

ALCL: anaplastic large cell lymphoma; ALL: anaplastic large cell lymphoma; BEAC: BCNU/carmustin, etoposid, cytarabin, cyclophosphamid; BEAM: BCNU, etoposide, cytarabine, melphalan; BCNU: carmustine; CHOP: cyclophosphamide, vincristine, doxorubicine, prednisone; Cy: cyclophosphamide; Mo: months; TBI: total body irradiation.

ter study that was the first that prospectively investigated the feasibility and efficacy of autotransplantation in newly diagnosed PTCL.¹⁸ Patients with primary cutaneous lymphomas and ALK-positive ALCL were excluded from the study. Four to six courses of CHOP were followed by DexaBEAM or ESHAP as stem cell mobilizing regimen. Myeloablative protocol consisted of hyperfractionated total body irradiation (TBI) and high-dose cyclophosphamide. The recently published data on the first 30 patients who entered the study showed an overall response rate after CHOP therapy of 80% [(43% complete remission (CR), 37% partial remission (PR)]. Twenty-one of 30 patients (70%) completed myeloablative therapy. At a median follow-up of 15 months 16 of 21 patients remained in CR. Six patients relapsed within a median time of 5.5 months after transplantation. In an intent-to-treat analysis, 9 of the 30 patients (30%) did not undergo autotransplantation mainly due to progressive disease. A recent update of our study confirmed these data.¹⁹ Of 65 evaluable patients almost two thirds (41/65) could be transplanted. After a median follow-up of 10 months after transplantation 28 out of 41 transplanted patients were in sustaining CR.

Two further phase II studies on this topic have been presented at the ASH Meeting and at the Lugano Meeting last year, both excluding primary cutaneous PTCL and ALK⁺ ALCL.^{20,21} The

Scandinavian trial consisted of 6 cycles CHOP followed by high-dose BEAM regimen. Thirty-three of the 47 patients (70%) underwent ASCT with a CR rate of 82% for the transplanted patients after a median observation of 17 months.²⁰ In the study by Lopez-Guillermo, an alternating regimen of high-dose CHOP and ESHAP was used.²¹ Of the 34 patients who were enrolled into the study only 41% received autotransplantation. In an intent-to-treat analysis the 4-year overall survival was 38% with a median follow-up for the survivors of 3.9 years (Table 1).

High-dose therapy and autotransplantation in relapsing or primary refractory PTCL

During the past 15 years, high-dose therapy with autologous SCT has shown favourable results in relapsing and primary refractory high-grade B-cell lymphomas and is accepted as the treatment of choice in this clinical situation for eligible patients. Prospective randomized studies on the effect of high-dose therapy as salvage therapy in PTCL are lacking, and only few retrospective studies addressed this issue and are listed in Table 2.²²⁻³⁰

In 1990, Vose *et al.* published data on the efficacy of high-dose therapy and autologous bone marrow transplantation in 41 patients with relapsed intermediate or high-grade B- and T-cell NHL.²² Myeloablative regimen was not stan-

Table 2. Studies on High-Dose Therapy and Autologous Stem Cell Transplantation in Peripheral T-cell Lymphomas as Salvage Therapy.

Author (year)	n	Regimen	Response	OS	Comment
Vose (1990) ²²	17	Diverse	59% CR	35% (2-year OS)	
Fanin (1999) ²³	64	Diverse	No data	70% (5-year OS)	Only ALCL
Haider (1999) ²⁴	14	Diverse	No data	74% (3-year OS)	Incl. alloSCT
Rodriguez (2001) ²⁵	29	Diverse	79% CR	39% (3-year OS)	Subgroup analysis
Blystad (2001) ²⁶	40	Diverse	80% CR	58% (3-year OS)	Incl. 1 st line therapy
Song (2003) ²⁷	36	Mel/Eto	42% CR	48% (3-year OS)	
Rodriguez (2003) ²⁸	78	Diverse	No data	45% (5-year OS)	Subgroup analysis
Jagasia (2004) ²⁹	28	Cy/Eto(Thio)	50% CR	69% (3-year OS)	Incl. primary cutaneous PTCL
Jantunen (2004) ³⁰	37	BEAC/BEAM	76% CR	54% (5-year OS) (35% non-ALCL) 63% in 1 st line 45% in 2 nd line	Incl. 1 st line therapy, TRM 16%

ALCL: anaplastic large cell lymphoma; Allo: allogeneic; BEAC: BCNU/carmustine, etoposid, cytarabine, cyclophosphamide; BEAM: BCNU, etoposide, cytarabine, melphalan; BCNU: carmustine; Cy: cyclophosphamide; Eto: etoposide; Thio: thiotepe.

standardized; high-dose regimen varied, and TBI was part of the myeloablative regimen in a subgroup of patients (23 of 41). Patients with T-cell lymphomas showed an actuarial 2-year overall survival and a 2-year disease-free survival (DFS) of 35% and 28%, respectively, which was equivalent to the long-term outcome in patients with B-cell NHL in the study.

Fanin *et al.* published retrospective data on 64 patients with ALCL treated with high-dose therapy and blood- or marrow-derived stem cell support.²³ Although this survey was restricted to ALCL, the cohort was rather heterogeneous. Pediatric patients were included in the study (median age, 25.2 years) and the status of ALK expression was not determined. Furthermore, 15 of 64 patients (23%) received transplantation in first remission, which is now considered an inappropriate approach in ALK-positive ALCL. The OS and the progression-free survival (PFS) of the whole population at five years was 70% and 56%, respectively. However, these results are biased by the patients aged < 20 years and patients receiving transplantation in first CR, who showed a significantly better outcome in a subgroup analysis.

Rodriguez *et al.* performed a retrospective single-center study on 36 patients with PTCL who received mainly autologous (n = 29) or allogeneic (n = 7) SCT after high-dose therapy as second-line therapy.²⁵ Seven patients with ALCL were included. The 3-year OS and PFS rates in the autologous group were 39% and 29%, respectively.

Blystad *et al.* investigated the outcome of 40 patients undergoing various high-dose regimens with autologous stem cell support, mainly at

chemosensitive relapse (n = 23) or in first remission, when > 1 chemotherapy regimen was needed to exhibit partial or complete remission (n = 13).²⁶ The remaining four patients had high-risk PTCL and received transplantation as first-line therapy. The 14 patients with ALCL who were included in the study showed a better OS compared with the other PTCL subgroups; however, this difference failed to reach statistical significance. The estimated OS for the entire group at 3 years was 58%, and the EFS was 48%. Of note, the authors reported a procedure-related mortality of 7.5%.

In another analysis of 36 patients with refractory disease, Song *et al.* found a 3-year OS and EFS of 48% and 37%, respectively, which did not differ from that found in 97 patients with high-grade B-cell lymphoma in a comparable analysis.²⁷ However, ALCL was included in the study, and a subgroup analysis showed a superior outcome of this entity that probably biased the overall results for PTCL.

The Spanish GEL-TAMO experience ASCT showed a 5-year OS of 45% in 78 patients with relapsing or refractory PTCL, including ALCL. There was no statistically significant difference between the patients transplanted in PR compared to the patients transplanted in second or subsequent CR.²⁸

Recently, Jantunen *et al.* published another series on autotransplantation as first-line or salvage therapy in 37 patients with PTCL including ALCL (n=14). The 5-year OS was 54% for the entire cohort. When autologous SCT was done as salvage treatment the 5-year OS was 45% compared with 63% in first-line therapy. In addition,

patients with ALCL had superior outcome compared to non-ALCL patients (5-year OS 85% versus 35%).³⁰

In summary, high-dose therapy followed by autotransplantation seems feasible with moderate toxicity that does not exceed toxicity of trials for other aggressive lymphomas. The impact of this approach as first-line therapy is still a matter of debate. One concern is the fraction of patients (about one third in intend-to treat analyses^{19,20}) that does not achieve autotransplantation due to prior progression of the disease under induction therapy. A recently published retrospective comparison did not find any benefit of high-dose therapy and ASCT compared to conventional treatment in the first-line setting.³¹ However, the regimen in the high-dose group was heterogeneous ranging from high-dose CHOP to allogeneic stem cell transplantation. In contrast, in the *International T-Cell Lymphoma Clinical/Pathologic Study* Vose *et al.* retrospectively revealed a significant better outcome for PTCL-undefined when autotransplanted compared to conventional treatment.³² To better define the role of autotransplantation randomised PTCL-restricted (multinational) studies are urgently needed.

Concerning salvage therapy, it also seems difficult to draw clear conclusions from the cited studies. Most series were rather small, and time for recruitment was long, ranging from 5 to 19 years. Furthermore, most studies included ALCL patient, which might bias the results. In addition, conditioning regimens are heterogeneous, and the value of TBI in this situation needs to be evaluated. However, the overall outcome for relapsing or refractory PTCL seems equivalent to the published data on high-grade B-cell NHL that is supported by at least two subgroup analyses. Therefore, myeloablative therapy followed by ASCT appears to be an appropriate approach in this clinical setting for PTCL.

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