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Abstract
Rescue chemotherapy or autologous stem cell transplantation (autoSCT) gives disappointing results in relapsed peripheral T-cell lymphomas (PTCLs). We have retrospectively evaluated the long-term outcome of 52 patients receiving allogeneic SCT for relapsed disease. Histologies were PTCL-not-otherwise specified (*n*=23), anaplastic large-cell lymphoma (*n*=11), angioimmunoblastic T-cell lymphomas (*n*=9) and rare subtypes (*n*=9). Patients were allografted from related siblings (*n*=33, 64%) or alternative donors (*n*=13 (25%) from unrelated and 6 (11%) from haploidentical family donors), following reduced-intensity conditioning (RIC) regimens including thiotepa, fludarabine and cyclophosphamide. Most of the patients had chemosensitive disease (*n*=39, 75%) and 27 (52%) failed a previous autoSCT. At a median follow-up of 67 months, 27 of 52 patients were found to be alive (52%) and 25 (48%) were dead (*n*=19 disease progression, *n*=6 non-relapse mortality (NRM)). The cumulative incidence (CI) of NRM was 12% at 5 years. Extensive chronic graft-versus-host disease increased the risk of NRM (33% versus 8%, *P*=0.04). The CI of relapse was 49% at 5 years, influenced by disease status at the time of allografting (*P*=0.0009) and treatment lines (*P*=0.007). Five-year overall survival and progression-free survival (PFS) were 50% (95% CI, 36 – 63%) and 40% (95% CI, 27 – 53%), respectively. The current PFS was 44% (95% CI, 30–57%). In all, 8 out of 12 patients (66%) who received donor-lymphocytes infusions for disease progression had a response. At multivariable analysis, refractory disease and age over 45 years were independent adverse prognostic factors. RIC allogeneic SCT is an effective salvage treatment with a better outcome for younger patients with chemosensitive disease.

Introduction

Peripheral T-cell lymphomas (PTCLs) account for 5–10% of all non-Hodgkin's lymphomas in the Western world and include entities that are heterogeneous in their biological and clinical characteristics.[1]
Patients affected by PTCL, other than anaplastic large-cell lymphomas (ALCLs) with anaplastic lymphoma-kinase expression, have a 5-year overall survival (OS) of approximately 25% with conventional chemotherapies. Unlike patients with diffuse large B-cell lymphomas, most of them do not benefit from anthracycline-based therapy as a part of their induction treatment or from abbreviated chemotherapy intervals. Consequently, intense therapeutic modalities, including autologous stem cell transplantation (autoSCT), were offered to these patients as consolidation of first remission or for relapsed/refractory disease. To date, few prospective studies have evaluated up-front autograft as consolidation of response.[2, 3, 4] Only patients achieving first complete remission appear to benefit from autoSCT, and studies with long-term follow-up have shown a disease-free survival ranging from 30 to 40%. Patients receiving autoSCT in second remission or with refractory disease have a poor outcome with a progression-free survival (PFS) ranging from 15–20% to 0%, respectively.[5, 6]
We firstly reported the activity of allogeneic stem cell transplantation (alloSCT), which now is increasingly used, supporting the evidence for a graft-versus-PTCL effect.[7, 8, 9] In a retrospective analysis, Kim *et al.*[7] reported a 2-year OS of 42% in a large population of patients with aggressive

non-Hodgkin's lymphomas receiving myeloablative alloSCT, with an especially good outcome for those with nodal PTCL. The efficacy of alloSCT was recently confirmed in a cohort of patients including several subtypes of PTCL; a better outcome was observed in angioimmunoblastic T-cell lymphoma (AITL), ALCL and PTCL not otherwise specified (PTCL-NOS) than for extranodal subtypes.[8]
Considering that myeloablative alloSCT carries a high risk of non-relapse mortality (NRM) between 20 and 45%, non-myeloablative or reduced-intensity conditioning (RIC) regimens have been widely used to reduce morbidity and mortality.
As the experience is limited by the analysis of a small series with a short-term follow-up, we performed an observational retrospective study on 52 patients receiving RIC alloSCT.

Patients and methods

Patient characteristics

Between June 1999 and March 2009, 52 patients were enrolled in a retrospective study involving 16 Italian hematology divisions. Majority of the patients (75%) had received alloSCT in the period 2003–2009. Only 17 of the 52 (33%) patients were updated in terms of clinical follow-up from a previously published study[9] (Table 1). The eligibility criteria were as follows: (i) diagnosis of nodal peripheral T-cell lymphoma; lymphoblastic lymphomas, Sezary syndrome and Mycosis fungoides were excluded; (ii) those in relapse after conventional chemotherapy or autoSCT or primary refractory disease were included; (iii) those who had undergone transplantation with a RIC regimen from related or unrelated donors were included.

Table 1 - Patients' characteristics.

		%
Median age at diagnosis (range)	47 years (15–64)	—
Sex (male/female)	33/19	64/37
Subtypes		
PTCL-NOS	23	45
AITL	9	17
ALCL	11	21
Other	9	17
Median time from Dx to AlloSCT (range)	18 (4–99 months)	—
No.of lines of treatment		
⩽2	34	65
>2	18	34
Previous autograft	27	52
Disease status at alloSCT		
CR/PR	39	75
Refractory	13	25
Donor type		
HLA-matched sibling	33	64
Unrelated/haploidentical	13/6	25/11
T-depletion		
No T-depletion	30	58
ATG	12	23
Alemtuzumab	10	19
Bone marrow involvement		
Yes	10	19
No	37	71
unknown	5	10
Extranodal disease		
Yes	24	46
No	23	44
unknown	5	10

Abbreviations: AITL, angioimmunoblastic T-cell lymphomas; ALCL, anaplastic large-cell lymphomas; alloSCT, allogeneic stem cell transplantation; ATG, anti-T-cell globulin; CR, complete remission; Dx, diagnosis; MUD, matched or mismatched unrelated donor; PR, partial remission; PTCL-NOS, peripheral T-cell lymphomas.

The median age was 47 years (range, 15–64). Approval was obtained from the Institutional Review Boards of the participating centers, and all of the patients gave their written informed consent. According to the World Health Organization (WHO) classification, the histological subtypes were as follows: 23 PTCL-NOS (45%), 11 ALCL (21%), 9 AITL (17%) and 9 with other histological subtypes (17%) (*n*=4 enteropathy-type T-cell, *n*=1 hepatosplenic T-cell lymphoma, *n*=1 non-nasal natural killer/T-cell lymphoma, *n*=1 nasal natural killer/T-cell lymphoma, *n*=1 subcutaneous panniculitis-like, *n*=1 primary cutaneous ALCL). Karnofsky performance was $\geqslant$80 in 43 cases (83%), <80 in 4 cases (8%) and unknown in 5 cases (9%). The median number of prior therapies was 2 (range, 1–4), with 17 patients (33%) having received only one previous line of treatment. Prior therapy included autoSCT in 27 cases (52%), and was the first line of treatment for these patients. At the time of alloSCT, most of the patients had chemosensitive disease (18 (35%) complete remission (CR), 21 (40%) partial remission), and 13 (25%) had refractory disease. The median time from diagnosis to transplantation was 18 months (range, 4–150 months), with 39 patients (75%) allografted more than 12 months after diagnosis.

We evaluated some prognostic factors (extranodal involvement, presence of bulky disease, bone marrow involvement and LDH level) with regard to disease burden before salvage therapy pre alloSCT. Overall 23 (44%) patients showed evidence of extranodal disease. Only two patients had evidence of bulky disease. In 10 patients we observed bone marrow involvement at the time of salvage therapy (19%). A high level of LDH before salvage therapy was reported in 14 patients ((24%), data missing in 14 patients).

Transplantation characteristics

A total of 33 (64%) patients received grafts from related siblings (30 from matched and 3 from one-antigen mismatched related siblings), 13 (25%) from matched or mismatched unrelated donors, and 6 (11%) from haploidentical family donors. All the patients received thiotepa-based RIC regimens. The stem cell source was bone marrow in 11 cases (21%) and peripheral blood in the remainder (*n*=41, 79%). *In vivo* T-depletion was used only in the case of alternative donors (*n*=22) and included rabbit anti-thymocyte globulin in 12 and alemtuzumab in 10 patients.

All of the patients allografted from related siblings received a RIC regimen containing thiotepa (10 mg/kg), cyclophosphamide (60 mg/kg) and fludarabine (60 mg/m^2).[4] In the case of related siblings, the graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A, adjusted to maintain blood levels of 200–300 ng/ml, and a short course of methotrexate (10 mg/m^2 on day +1, and 8 mg/m^2 on days +3 and +6). All 13 patients allografted from a well-matched (*n*=7 (10/10)) or mismatched (*n*=4 (9/10); *n*=2 (8/10)) unrelated donor received a combination of thiotepa (10 mg/kg) and cyclophosphamide (100 mg/kg) (*n*=10) with or without fludarabine (120 mg/m^2) (*n*=3).[10] The grafts were depleted of T-cells using rabbit anti-thymocyte globulin (Thymoglobulin 3.5 mg/kg/day on days −4 and −3) or alemtuzumab in 11 and 2 cases, respectively. Post-transplantation GVHD prophylaxis consisted of cyclosporine A and short-course methotrexate (10 mg/m^2 on day +1, and 8 mg/m^2 on days +3 and +6).

Donor lymphocyte infusions (DLIs) were given in case of progressive disease. The starting dose for DLI was decided according to donor type and time between allograft and the first dose. Patients with progressive disease after alloSCT from sibling donors received 1 or 5 × 10^{6}CD3+/kg donor lymphocytes if acute GVHD or response has not occurred within 4 weeks from withdrawal of immunosuppressive therapy. After 4 weeks (in absence of GVHD or response), patients received a second dose containing 1 × 10^{7}CD3+/kg donor lymphocytes. In case of unrelated donors, patients received 1 or 5 × 10^{5}CD3+/kg donor lymphocytes, if acute GVHD or response has not occurred within 4 weeks from withdrawal of immunosuppressive therapy. After 4 weeks (in absence of GVHD or response), patients received a second dose containing 1 × 10^{6}CD3+/kg donor lymphocytes.

All the six patients allografted from haploidentical donors underwent conditioning with thiotepa (10 mg/kg), cyclophosphamide (60 mg/kg) and fludarabine (120 mg/m^2), and total body irradiation (2 Gy). CD34+ cell selection and alemtuzumab treatment (15 mg/m^2 on day −2) were used for *ex vivo* and *in vivo* T-cell depletion.[11] The majority of the patients allografted from haploidentical donors (four out of six) received pre-emptive CD8-depleted DLIs, to prevent infectious complications according to a dedicated protocol for haplo-SCT.

Historical comparison: patients affected by diffuse large B-cell lymphoma (DLBCL) allografted from HLA-identical donors

The 33 patients, affected by PTCL, who received grafts from related siblings were retrospectively compared with 34 patients with DLBCL allografted by the same Italian Hematology centers between February 1999 and June 2008.
All the patients were allografted from related siblings using the same RIC regimen containing thiotepa, fludarabine and cyclophosphamide (Supplementary Table 1).

Response criteria and statistical analysis

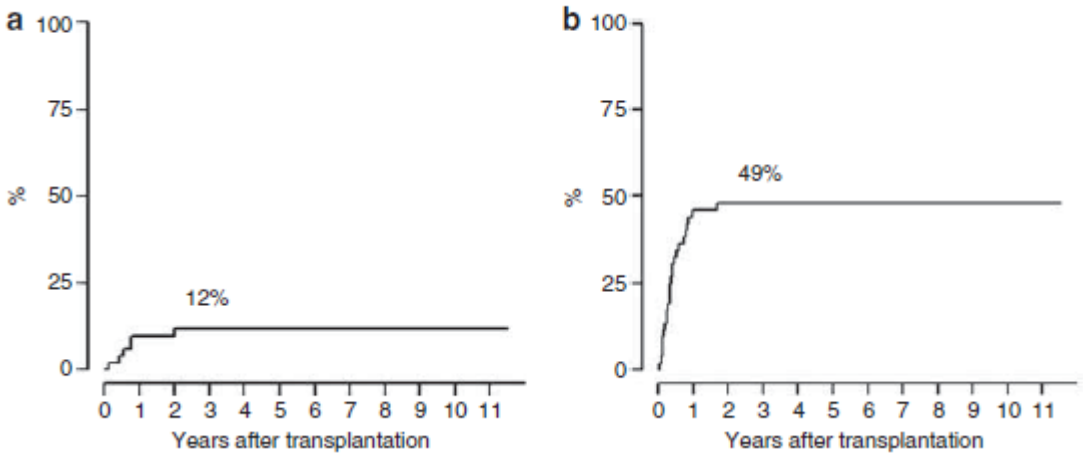
The response to therapy was evaluated in each center at 1,3 and 6 months after alloSCT and every 6 months thereafter. Response to treatment was evaluated using the International Workshop non-Hodgkin's lymphomas criteria.[12] Acute GVHD and chronic GVHD were evaluated using the criteria previously described by Przepiorka *et al.*[13]
The OS and PFS curves were estimated using the Kaplan–Meier method and compared by means of the log-rank test. Patients who responded to DLIs without subsequent progression at the time of the analysis were censored at the last follow-up date in the analysis of current PFS.
The multivariate analyses were performed using Cox regression models.[14] The occurrence of NRM, relapse, and acute and chronic GVHD was calculated using cumulative incidence (CI) estimates.[15] In the estimation of GVHD, death without GVHD was evaluated as a competing event.
The statistical analyses were done using the software R version 2.10.1.

Results

NRM and GVHD

Only five patients died of NRM at a median time of 9 months (range, 5–24); there was only one late death for encephalitis 24 months from transplantation. A total of three patients died after alloSCT from a matched related sibling and two from an alternative donor (*n*=1 from mismatched unrelated donors, *n*=1 haploidentical donor). The estimated 5-year NRM was 12% (Figure 1). The causes of NRM were multi-organ failure (*n*=1), chronic GVHD (*n*=1) and infections (*n*=3). All the patients who died of NRM experienced acute (*n*=2) or chronic (*n*=3, one limited and two extensive) GVHD. The occurrence of extensive GVHD significantly increased the risk of NRM (33% versus 8%, *P*=0.04) (Supplementary Figure 1).

Figure 1. CI of non-relapse mortality (a) and relapse (b) after allogeneic stem cell transplantation.



All patients were evaluable for acute GVHD; only 11 developed grade II–IV (*n*=7 grade II; *n*=4 grade III–IV), with an estimated crude cumulative incidence of 22%. A total of 47 patients were evaluable for chronic GVHD (5 patients were not evaluable for early deaths); it was limited in 9 and

extensive in 3 patients, with an estimated crude cumulative incidence of 27%. A total of 16 patients received DLIs; acute and chronic GVHD occurred in 5 and 9 patients (*n*=6 limited (*n*=4 *de novo*), *n*=3 extensive), respectively. Overall, the CI of acute and chronic GVHD increased after DLIs: 31% and 47%, respectively. Interestingly, of the 21 patients experiencing chronic GVHD, 13 (62%) achieved long-term remission. However, the development of chronic GVHD did not have any statistically significant impact on relapse risk (RR) (40% versus 51%, *P*=0.37).

Relapse

The crude cumulative incidence of relapse was 33% at 6 months and 49% at 5 years (Figure 1). Overall, 25 patients (48%) relapsed with a median time to progression of only 4.5 months (range, 1–20 months). Of the 25 relapsing patients, 19 (76%) died of disease progression at a median time of 8 months from alloSCT (range, 2–38.6) and only 6 are still alive (all but one received DLIs). Relapse occurred in 15 of 33 (45%) patients allografted from matched related siblings and in 10 of 19 (52%) of those allografted from alternative donors. Disease relapse occurred in 4 of 18 (22%) patients transplanted in CR and in 11 of 21 (53%) of those in partial remission. Therefore, there was a statistically significant difference in RR between those allografted in complete remission and those in partial remission (24% versus 54%, *P*=0.02). From the 13 patients characterised as refractory at alloSCT, only 3 patients are still alive; the remaining died of disease progression. Patients allografted with refractory disease had a higher RR than those with chemosensitive disease (77% versus 40% at 5 years, respectively; *P*<0.0009). In addition, the RR was higher in patients treated with more than two lines of chemotherapy before alloSCT (72% versus 37% at 5 years, *P*=0.007). The type of donor, age and failure of autoSCT, and time between diagnosis and allograft did not affect RR (Table 2).

Table 2 - Crude cumulative incidence of relapse.

	CI relapse(%)	P
Age (years)		
⩽45	43	0.47
>45	54	
No. of lines of treatment		
⩽2	36	**0.007**
>2	72	
Previous autoSCT		
No	41	0.23
Yes	57	
Disease status		
Sensitive	40	**0.0009**
Refractory	77	
Dx to alloSCT (months)		
⩽12	74	**0.08**
>12	42	
Donor type		
HLA-matched sibling	46	0.49
Alternative	59	

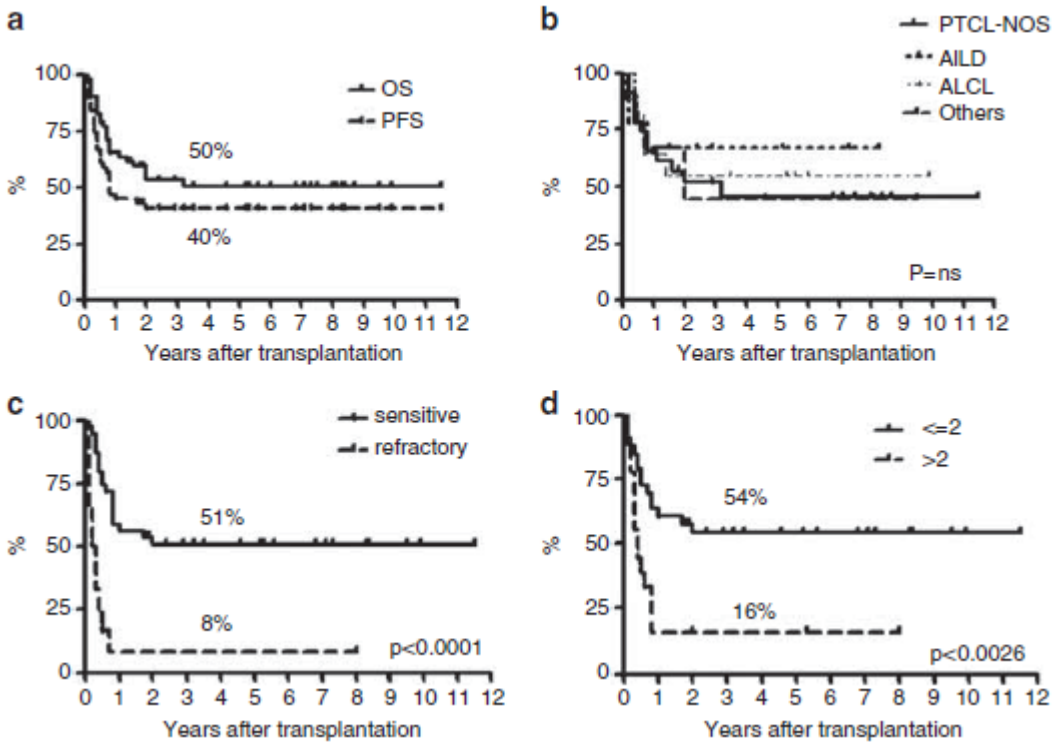
Abbreviations: AlloSCT, allogeneic stem cell transplantation;.AutoSCT, Autologous stem cell transplantation; CI, crude cumulative incidence; Dx, diagnosis; NRM, non-relapse mortality.
Bold values are statistically significant.

Univariate and multivariate analysis for PFS and OS

In all,27 (52%) of the 52 patients are currently alive, with a median follow-up of surviving patients of 67 months (range 18–138 months). The estimated 5-year PFS and OS are 40% (95% CI, 27–53%) and 50% (95% CI, 36–63%), respectively (Figure 2). The current PFS was 44% (95% CI, 30–57%).

Figure 2. Progression-free survival and overall survival (a) and overall survival according to histotype (b) 66% angioimmunoblastic T-cell lymphoma (AITL), 54% anaplastic large-cell

lymphoma (ALCL), 45% PTCL not otherwise specified (PTCL-NOS) and 44% for other subtypes; Progression-free survival according to disease status (c) and number of treatment lines before allograft (d).



Five-year PFS and OS were as follows in different subtypes: 39% (95% CI, 20–58%) and 45% (95% CI, 24–64%) for PTCL-NOS, 44% (95% CI, 14–71%) and 66% (95% CI, 28–87%) for AITL, 45% (95% CI, 17–70%) and 54% for ALCL (95% CI, 23–70%), and 37% (95% CI, 9–66%) and 44% for other subtypes (95% CI, 14–71%). We did not observe a significant difference in the outcome between the different histotypes (Figure 2).

The results of univariate analysis are given in Table 3. Chemosensitive disease was associated with a better PFS (51% versus 8%, $P<0.0001$) and OS (59% versus 23%, $P=0.002$). Moreover, patients under 45 years had better OS than older ones (68% versus 34%, $P=0.012$). Patients pre-treated with fewer lines of treatment (≤ 2) experienced better PFS (54% versus 16%, $P<0.0026$). The outcome of patients transplanted from haploidentical donors is given in Supplementary Table 2.

Table 3 - Univariate analysis for overall and progression-free survival.

	OS (%)	CI (%)	P	PFS (%)	CI (%)	P
Global	50	36–63	—	40	27–53	—
Age (years)						
⩽45	68	44–83	**0.012**	53	31–71	0.14
>45	34	16–53		26	11–44	
Subtypes						
PTCL-NOS	45	24–64	0.91	39	20–58	0.97
AITL	66	28–87		44	14–71	
ALCL	54	23–77		45	17–70	
Other	44	14–71		37	9–66	
No. of lines of treatment						
⩽2	56	37–71	0.45	54	36–69	
>2	39	16–61		16	4–35	**0.0026**
Previous autoSCT						
No	47	26–66	0.80	46	26–64	0.31
Yes	53	32–70		31	15–49	
Disease status						
Sensitive	59	41–74	**0.002**	51	35–65	<**0.0001**
Refractory	23	5–47		8	1–30	
Dx to alloSCT (months)						
⩽12	26	7–51	0.06	18	3–43	0.09
>12	58	40–72		42	26–57	
Donor type						
HLA-matched sibling	52	34–67	0.63	41	24–57	0.62
Alternative	43	17–67		24	5–51	

Abbreviations: AITL, angioimmunoblastic T-cell lymphomas; ALCL, anaplastic large cell lymphomas; AlloSCT, allogeneic stem cell transplantation; Auto, autologous stem cell transplantation; Dx, diagnosis; OS, overall survival; PFS, progression-free survival; PTCL-NOS, peripheral T-cell lymphomas; The estimates are given in percentages at 5 years from allografting.
Bold values are statistically significant.

In a multivariate analysis for OS, older age and chemoresistant disease at the time of alloSCT had a significant negative prognostic impact on OS (increased risk of death of 6.9 (P<0.001) and 5 (P<0.002), respectively) and PFS (increased risk of failure of 3.1 (P=0.01) and 5 (P<0.0003), respectively) (Table 4). Patients allografted more than 12 months after diagnosis had a trend for a reduced risk of failure (reduced risk of failure of 0.36 (P=0.06)). The status of bone marrow involvement and extranodal disease did not influence the outcome in univariate and multivariate analysis (data not shown).

Table 4 - Multivariable analyses of overall and progression-free survival by Cox regression models.

Variable	OS		PFS	
	Hazard ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age (years)				
⩽45	1	**0.001**	1	**0.01**
>45	6.90		3.17	
Subtypes				
AITL	1	0.76	1	0.82
Others	0.82		1.12	
No. of Lines of treatment				
⩽2	1	0.59	1	0.09
>2	1.3		2.06	
Previous autoSCT				
No	1	0.42	1	0.06
Yes	1.49		2.5	
Disease status				
Sensitive	1	**0.002**	1	<**0.0003**
Refractory	5		5	
Dx to alloSCT (months)				
⩽12	1	0.26	1	0.06
>12	0.54		0.36	
Donor type				
HLA-matched sibling	1	0.82	1	0.97
Alternative	0.90		0.98	

Abbreviations: AlloSCT, allogeneic stem cell transplantation; Auto, autologous stem cell transplantation; Dx, diagnosis; GVHD, graft-versus-host disease; OS, overall survival; PFS, progression-free survival.
Bold values are statistically significant.

Responses to DLIs

DLIs were given to those who relapsed (*n*=12) or to those whose immune reconstitution was boosted (*n*=4) when haploidentical donors were used. Five patients were treated with chemotherapy (*n*=4) or radiotherapy (*n*=1) before DLIs. Overall, 8 of 12 patients (66%) treated for disease progression had a response (5 complete and 3 partial). Subtypes of patients achieving CR were heterogeneous (*n*=2 PTCL-NOS, *n*=1 cutaneous, *n*=1 AITL, *n*=1 ALCL anaplastic lymphoma kinase positive). All the five patients who had a CR after DLIs are alive (three still in complete remission) after a median time of observation of 5 years (range, 2–8 years) after the last dose of lymphocytes. All the three patients who had a partial response subsequently progressed and died.

Comparison of outcome between DLBCL and PTCL allografted from matched-related siblings

There was no statistically significant difference in OS at 5 years between patients with relapsed DLBCL and those with PTCL (69% versus 53%, *P*=0.23). The 5-year PFS was 55% for patients with DLBCL and 41% for those with PTCL (*P*=0.26).

Discussion

There are very few data on the long-term follow-up of patients receiving RIC alloSCT or DLIs for relapsed/refractory PTCL. In this study, we confirm and expand our previous observation on the evidence of a graft-versus-T cell lymphoma effect.[9] Overall 50% of the patients are alive at a median follow-up of 67 months, suggesting a potentially curative role for this salvage strategy. Most of the patients with relapsed PTCL had a limited benefit following autoSCT. The Spanish group showed that patients autografted in second partial remission or with refractory disease had a 5-year PFS of 23% and 10%, respectively. In addition, patients with an age-adjusted international prognostic index of more than 1 and/or high β2-microglobulin had a PFS of 24%.[5] The administration of uncontaminated stem cells using purged autograft did not improve the outcome of patients with relapsed or refractory disease with a PFS<15%.[6]

In recent years, alloSCT has been investigated in patients suffering from aggressive lymphomas who failed autoSCT or who were unable to receive it. In a large retrospective analysis on 111 aggressive lymphomas with 51 PTCL patients, the authors reported a 2-year OS of 42% following a myeloablative conditioning. Interestingly, patients with PTCL had better survival than those with DLBCL, suggesting that T-cells can be a good target for donor-derived immune cells. Few studies have focused on patients affected by T-cell malignancies. Le Gouill *et al.*[8] recently analyzed the long-term outcome (median follow-up 43 months) of 77 patients with several subtypes of PTCL, most of whom were allografted with myeloablative conditioning (74%) and from HLA-matched sibling donors (78%). Interestingly, the 5-year OS of 57% did not change significantly in different histotypes and the prognosis was also encouraging in those with chemoresistant disease (29% at 5 years).

Despite the low RR reported in the above-mentioned studies, the NRM ranged from 30 to 40%, leading to the development of better supportive care and RIC regimens.[16] One recent analysis performed by Gooley *et al.*[17] indicated that there was a reduction in overall mortality from 41 to 26% in the period 2003–2007 as compared with 1993–1997 period, because of changes in acute GVHD treatments and in a better management of infectious complications. Most of the studies performed to date have also shown that RIC regimens are associated with a reduced NRM; therefore this strategy can be offered to elderly or heavily pre-treated patients. In addition, the availability of RIC regimens has made it feasible to perform alloSCT after a failed autoSCT without a substantial increase of toxicity. The only concern regarding the use of RIC or nonmyeloablative regimens was related to a possibly higher RR, as it has been described in patients allografted for chronic lymphocytic leukemia and Hodgkin's lymphomas.[18, 19]

In our study, all the patients were allografted following a RIC regimen with a limited NRM. Interestingly, we did not observe a significant difference between the CI of NRM for patients allografted from matched siblings and those allografted from alternative donors. A number of issues should be mentioned: first, the median age of the patients allografted from haploidentical donors (39 years) was far lower than those allografted from matched-sibling donors; second, the recent introduction of high-resolution HLA typing has improved the outcome of patients allografted from unrelated donors. Indeed, Michallet *et al.*[20] have observed the same outcome (in terms of OS and NRM) between patients with CLL allografted from HLA-identical siblings and those allografted from well-matched (8/8 high resolution) unrelated donors. Previous studies showed that Karnofsky performance status was closely related to NRM and OS.[21] Most of our patients (83%) had a good Karnofsky performance status that probably reduced the risk of NRM.

Several factors suggest that alloSCT may overcome the unfavorable prognostic impact of T-cell phenotype and confirmed the existence of a 'graft-versus-lymphoma effect': first, we observed a plateau in the PFS and OS curves after the first 36 months that was not observed with other treatments; second, we did not observe a statistically significant difference in outcome between patients allografted with a diagnosis of PTCL and DLBCL; and third, some patients experienced long-lasting responses to DLIs.

A recent study explored an alloSCT after a non-myeloablative conditioning regimen containing fludarabine and low-dose TBI. The conversion from partial remission to CR after such reduced

conditioning further supported the existence of a 'graft-versus lymphoma' effect.[22] A retrospective study conducted by Dana Farber Cancer Institute explored the outcome of patients undergoing allotransplant following myeloablative (60%) or RIC regimens (40%) over a 12-year period. Interestingly, the risk of relapse with RIC was higher than that with myeloablative conditioning, but the OS and PFS were similar.[23]

Our study is the largest retrospective study with a rather long follow-up, including only patients allografted following a RIC regimen. Of note, the patients have been treated with homogeneous conditioning regimens mainly based on the use of thiotepa and cyclophosphamide. We have included several patients who failed a previous autoSCT, and we reported clinical activity also in those patients who usually have a median OS of less than 12 months with other treatments.

Patients affected by aggressive non-Hodgkin's lymphomas may relapse rapidly after alloSCT and frequently DLIs are ineffective. In this study, we showed that some patients with an early relapse had long-lasting complete remissions following DLIs suggesting that this type of lymphoma is sensitive to the so-called 'graft-versus-lymphoma effect'. Experience with DLIs in such type of lymphoma is limited; some responses have been reported in AITL[24] and in cutaneous T-cell lymphomas.[23]

In this report and in the study performed by Le Gouill *et al.*,[8] a non-significant trend for a better outcome was observed in the patients with AILT. In fact, the recent study performed by Kyriakou showed a very low RR (20% at 3 years), suggesting that this subtype is probably more susceptible to the graft-versus-lymphoma effect.[24]

Despite the defined role of alloSCT, supported by our work and by others,[8, 23, 24] it is important to understand when and how to use it. A reduced RR was observed in less heavily pretreated patients, suggesting that allograft should be introduced earlier in the salvage strategy before the occurrence of chemoresistance. AlloSCT can be considered also in patients affected by primary refractory disease; we have shown that the 5-year OS for refractory disease patients was 23%. In the near future, the use of novel drugs could 'bridge' the patients- to –transplant gap in a condition of partial or complete response. It has to be explored in clinical trials whether early withdrawal of immunosuppression can help a more rapid exploitation of the graft versus lymphoma effect.

Given the rarity of PTCLs, the majority of patients should be enrolled in clinical trials. At present, we do not know the prognostic factors to predict early failure or long-term remissions. Despite a limited knowledge regarding the main molecular pathways involved in the pathogenesis of PTCL, new drugs such as histone deacetylase inhibitors, mammalian target of rapamycin inhibitors and monoclonal antibodies are under investigation in relapsed disease, with overall responses ranging from 15 to 30%. The identification of new drugs would probably decrease early failures and, in the future, more patients will be able to receive alloSCT in partial or complete remission.

Conflict of interest

The authors declare no conflict of interest.

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