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ORIGINAL ARTICLE

Effect of immune modulation in relapsed peripheral T-cell lymphomas after post-allogeneic stem cell transplantation: a study by the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC)

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Peripheral T-cell lymphoma carries a poor prognosis. To document a possible graft-versus-lymphoma effect in this setting, we evaluated the impact of immunomodulation in 63 patients with peripheral T-cell lymphoma who relapsed after allogeneic transplant in 27 SFGM-TC centers. Relapse occurred after a median of 2.8 months. Patients were then treated with non-immunologic strategies (chemotherapy, radiotherapy) and/or immune modulation (donor lymphocyte infusions (DLI) and/or discontinuation of immunosuppressive therapy). Median overall survival (OS) after relapse was 6.1 months (DLI group: 23.6 months, non-DLI group: 3.6 months). Among the 14 patients who received DLI, 9 responded and 2 had stable disease. Among the remaining 49 patients, a complete response accompanied by extensive chronic GvHD was achieved in two patients after tapering of immunosuppressive drugs. Thirty patients received radio-chemotherapy, with an overall response rate of 50%. In multivariate analysis, chronic GvHD (odds ratio: 11.25 (2.68–48.21), $P = 0.0009$) and skin relapse (odds ratio: 4.15 (1.04–16.50), $P = 0.043$) were associated with a better response to treatment at relapse. In a time-dependent analysis, the only factor predictive of OS was the time from transplantation to relapse (hazards ratio: 0.33 (0.17–0.640), $P = 0.0009$). This large series provides encouraging evidence of a true GvL effect in this disease.

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INTRODUCTION

Peripheral T-cell lymphomas (PTCL) account for 10–15% of non-Hodgkin lymphomas and constitute a heterogeneous group of histological entities. Because PTCL is frequently resistant to standard chemotherapy, the prognosis is generally poor: the overall 5-year overall survival (OS) rate among patients treated with conventional chemotherapy ranges from 25% to 45%.[1] Autologous stem cell transplantation is frequently used in eligible patients but relapse is frequent, especially in the case of chemoresistance at transplantation.[2] Allogenic SCT (allo-SCT) is increasingly used as an alternative strategy, based on a potent graft-versus-lymphoma effect (GvL). However, data from retrospective[3–11] and prospective non-randomized studies[12] are insufficient to recommend allo-SCT as first-line treatment. The European Bone Marrow Transplantation Society currently considers allo-SCT to be an option for selected patients with chemosensitive disease in first or second complete response (CR), if a sibling or unrelated HLA-matched donor is available (grade 2 recommendations). In other situations the use of allo-SCT should be restricted to clinical trials. Three-year event-free survival rates

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range from 40% to 60% after allo-SCT, and disease control before SCT is the main prognostic factor. The impact of conditioning intensity is difficult to assess. Indeed, OS is similar with a reduced-intensity regimen (RIC) and a myeloablative-conditioning regimen, but the former is associated with a higher relapse rate and the latter with a higher risk of toxic death.

There is some evidence of a GvL effect in PTCL. First, relatively good results have been obtained with RIC,[12] likely more to an immunological effect than to more-intensive chemotherapy. Second, in most studies the survival curve stabilized after 12–18 months, suggesting a possible curative effect.[4] Third, chronic GvHD has been linked to a lower risk of relapse.[5] Finally, a negative impact on survival, due to a high relapse rate (70%), has been reported with T-cell-depleted grafts in primitive cutaneous T-cell lymphoma (TCL).[7] Few data are available on treatment options after PTCL relapse. In an Italian series, 76% of 25 patients who relapsed after transplantation died, within a median of 8 months.[5] Some responses have been reported after immunomodulation based on tapering of immunosuppressive drugs and/or on donor lymphocyte infusion (DLI).[4–8,13,14]

To better assess the possible GvL effect in PTCL, we studied 63 patients who relapsed after allo-SCT, focusing on the impact of immunomodulation based on tapering of immunosuppressive drugs and/or DLI on subsequent outcome.

PATIENTS AND METHODS

Study design, inclusion criteria, data collection and definitions

This multicenter retrospective study was based on the SFGM-TC registry. Patients with PTCL who underwent allo-SCT in 27 centers (26 French and one Belgian) between January 1988 and December 2012 were included if they experienced relapse or progression. Patients younger than 15 years at SCT and those with insufficient data or <6 months of follow-up were excluded. The study was approved by the SFGM-TC scientific council. When needed, local investigators collected clinical and biological data from the patients' files, up to 23 February 2014. Informed consent from patients was obtained in accordance with the Declaration of Helsinski. A CR was defined by the disappearance of all clinical, radiological and laboratory evidence of disease. A partial response (PR) was defined as a reduction in tumor mass of 50%. Progressive disease was defined by an increase in tumor mass of $>25\%$. Other patients were classified as having stable disease. Relapse was defined as clinical or radiological signs of disease recurrence. Two types of relapse were distinguished: cutaneous relapse in the absence of constitutional symptoms, a tumor syndrome or abnormal blood cells; and systemic relapse in all other cases. GvHD was graded according to international criteria (grade 0, I, II, III or IV for acute GvHD, and 'limited' or 'extensive' for chronic GvHD).[15]

At relapse, the patients received standard chemotherapy, radiation therapy or local treatment (retinoic acid, PUVA-therapy), or immunomodulation based on a reduction or discontinuation of immunosuppressive drugs and/or DLI. The choice of treatment was made by the clinician taking care of the patient, according to local practices. Two groups were compared retrospectively, namely patients who did and did not receive DLI.

Statistical analysis

Descriptive data are expressed as percentages for qualitative data and as median and range for quantitative data. Overall survival was defined as the time from relapse to date of death or date of last follow-up. OS was estimated by the Kaplan–Meier method. A univariate analysis was performed for OS using Cox proportional hazards model.

In survival analysis, exposure that appears during the follow-up must be taken into account as a time-dependent covariate in the Cox proportional hazards model. Here, DLI and chronic GvHD were included as a time-dependent covariate for OS analysis. Interactions were tested between chronic GvHD and DLI. All factors with $P<0.20$ at univariate analysis were included in a multiple Cox model with forward selection. Univariate and multivariate analysis of variables predictive of the response to relapse therapy was based on logistic regression. All tests were two-sided at a 0.05 significance level. Statistical analyses were performed using the R statistical software version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org).

RESULTS

Patient characteristics

Patient characteristics are detailed in Table 1. Among the 373 patients who received an allograft for PTCL during the study period (1988–2012), 76 patients who relapsed met the inclusion criteria (20.3%). Thirteen of these patients were excluded (one died on post transplant day 1, and data were insufficient in 12 cases). The study population thus consisted of 63 patients.

Median age was 44 years (16–68 years) at transplantation, and 67% of the patients were male. The main histopathology subtypes (WHO classification) were T-cell 'not otherwise specified ($n=20$, 32%), primary cutaneous TCL ($n=13$, 21%) and anaplastic large cell lymphomas (ALCL, $n=11$, 17%). Other subtypes were angioimmunoblastic TCL (AITL $n=8$), T/NK lymphomas ($n=5$), adult T-cell lymphomas ($n=5$) and enteropathy-associated T lymphomas ($n=1$).

All 13 patients with primary cutaneous TCL had advanced-stage disease at transplantation (IIB: $n=2$, III: $n=1$, IV: $n=9$, non-available data: $n=1$) according to the ISCL/EORTC (International Society for Cutaneous Lymphomas/ European Organization of Reseach and Treatment of Cancer) classification.

The patients had received a median of two lines of treatment before allo-SCT (range: 1–8), including auto-SCT in 16 cases (25%). Allo-SCT was performed a median of 12.8 months after diagnosis (range: 2.9–147 months). At transplantation, 24 patients (38%) were in CR (including seven CR1), 27 were in PR (43%) and 12 had progressive disease (19%).

Transplant procedures

Forty patients received RIC regimen and 23 received a myeloablative regimen. T-cell depletion of the graft was not performed. The stem cell source was bone marrow ($n=9$), PBSCs ($n=47$) or cord blood ($n=7$). The donors were HLA-identical siblings ($n=32$), matched unrelated donors ($n=12$), mismatched unrelated donors ($n=11$), cord blood units ($n=7$) or haploidentical donor ($n=1$).

Outcome after allo-SCT and relapse characteristics

The median time from allo-SCT to relapse was 2.8 months (interquartile range 25–75: 1.6–6.2). Half the patients developed acute GvHD before relapse (grade 3–4 in 12%). Seventy-five percent of the relapses occurred during the first 6 months post transplant. Chimerism at relapse, available in 40% of cases, was donor type in 17 cases, mixed type in five cases and recipient type in three cases. Relapse was limited to the skin in 30% of cases. At the time of relapse, 71% of the patients were still receiving immunosuppressive drugs.

Treatment at relapse

Relapse treatments and responses to treatments are described in Figure 1.

Treatments and responses in the DLI group

Fourteen patients (22%) received a total of 19 DLI. Their characteristics are described in Table 1, and details of their treatment in Table 2. The median time between allo-SCT and relapse was 123 days (range, 27–560 days). The histological subtypes were T-cell 'not otherwise specified ($n=5$), ALCL ($n=3$), T/NK TCL ($n=2$), mycosis fungoides ($n=2$), Sézary syndrome ($n=1$) and adult T-cell lymphoma ($n=1$). Five relapses were limited to the skin (two ALCL, one T/NK, one T-cell 'not otherwise specified and one mycosis fungoide). Acute GvHD occurred before

Table 1. Patients' characteristics

	DLI group (n = *14*)	*Non DLI group* (n = *49*)	P-*value*
Gender			
Male (%)	10 (71.4%)	32 (65.3%)	0.76
Age at transplant (years)			
median (IQR)	43 (34.5–55)	47 (35–56)	0.79
Histologic subtypes			
AITL	0 (0%)	8 (16.3%)	0.56
TCL NOS	5 (35.7%)	15 (30.6%)	
ALCL	3 (21.4%)	8 (16.3%)	
MF	2 (14.3%)	8 (16.3%)	
EATL	0 (0%)	1 (2.0%)	
NK nasal	1 (7.1%)	3 (6.1%)	
NK non-nasal	1 (7.1%)	0 (0%)	
ATL	1 (7.1%)	4 (8.1%)	
Sézary	1 (7.1%)	2 (4.1%)	
Disease status at transplant			
CR	7 (50%)	17 (34.7%)	0.45
PR	4 (28.6%)	23 (46.9%)	
PD	3 (21.4%)	9 (18.4%)	
Conditioning regimen			
MAC	4 (28.6%)	19 (38.8%)	0.7
RIC	10 (71.4%)	30 (61.2%)	
aGvHd before relapse			
Grade 1–2	6 (42.9%)	20 (40.8%)	0.58
Grade 3–4	1 (7.1%)	3 (6.1%)	
cGvHd			
Limited	2 (14.3%)	7 (14.3%)	0.81
Extensive	3 (21.4%)	7 (14.3%)	
Time transplant relapse (days)			
Median (IQR)	123 (68.25–349.8)	81 (47–164)	0.14
Skin relapse			
Yes	5 (41.7%)	12 (27.3%)	0.48
Cytoreductive treatment			
Yes	9 (64,3%)	30 (61,2%)	1
Disease status at last follow-up			
CR	3 (21.4%)	8 (16.3%)	0.27
PR	1 (7.1%)	0 (0%)	
s.d.	1 (7.1%)	2 (4.1%)	
PD	9 (64.3%)	39 (79.6%)	
Median follow-up (days)			
median (IQR)	537.5 (200.51579)	99 (29–251)	0.0002

Abbreviations: aGvH = acute graft versus host disease; AITL = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large-cell lymphoma; CR = complete response; cGvHd = chronic graft versus host disease; DLI = donor lymphocyte infusion; EATL = enteropathy-associated T lymphoma; IQR = interquartile range; MAC = myeloablative regimen; MF = mycosis fungoide; PD = progressive disease; PR = partial response; RIC = reduced-intensity regimen; s.d. = stable disease; T NHL NOS = T-cell non Hodgkin lymphoma 'not otherwise specified'.

relapse in 51% of these patients (grade 1 ($n=1$), grade 2 ($n=4$), grade 3 ($n=0$), grade 4 ($n=1$)). Nine patients received prior or concomitant cytoreductive treatment, consisting of chemotherapy ($n=7$), radiotherapy ($n=1$) or both ($n=1$). The median time between relapse and the first DLI was 60 days (range, 13–163 days). The median total dose of DLI was 20×10^6 $CD3^+$ cells/kg. The donor was an HLA-identical sibling ($n=8$), an unrelated matched donor ($n=4$) or an unrelated mismatched donor ($n=2$).

Nine out these 14 patients responded to DLI (7 CR, 2 PR) and the disease stabilized in 2 patients. The overall response rate (PR+CR +stable disease) was 78%.

The response rate was 7/9 for patients treated with DLI plus another treatment and 4/5 for patients who received DLI alone, which suggests an effectiveness of immune modulation, though the number of patients is too small to formally conclude. Details of associated treatments are available in Table 2. It should be noted that no patient in the DLI– group received anti-CD30 therapy at first post transplant relapse, but one patient with T-NOS lymphoma was treated with brentuximab for a second post DLI relapse, with a long-lasting response and no sign of GvHD.

Acute GvHd occurred in six patients after DLI. All five patients who developed chronic GvHD after DLI responded (four CR and one PR) compared with six of the nine patients who did not develop GvHD (three CR, one PR, two stable disease). All five patients with isolated cutaneous relapse responded to DLI (three CR, one PR, one stable disease).

Treatments and responses in the group without DLI

Forty-nine patients did not receive DLI at relapse. The median time between transplantation and relapse in this group was 81 days (range, 17–2149 days). Nineteen patients (30%) received no other treatment at relapse than withdrawal of immunosuppressive drugs. Two of these latter patients (one AITL[16] and one Sézary) had a durable clinical response (30 and 22 months at last follow-up), associated with extensive chronic GvHD. Thirty patients received salvage treatment consisting of chemotherapy ($n=20$), chemotherapy and radiotherapy ($n=5$), PUVA or another local treatment ($n=3$) or radiotherapy ($n=2$). Thirteen of them (43%) responded to this treatment (nine CR, four PR) and two had stable disease, giving an overall response rate of 50%. Among the 25 patients who received chemotherapy at relapse, salvage regimens were various, containing alkylating agents, anthracyclines, alkaloid agents, anti-metabolite agents, anti-CD56 therapy, bortezomib, anti-CD30 therapy or corticosteroids. We report two patients who received brentuximab (one ALCL ALK+ lymphoma and one with T-NOS lymphoma with relapse limited to the skin) and both entered prolonged CR.

Survival and factors predictive of OS and the treatment response

Median OS was 6.1 months (DLI group: 23.6 months, non-DLI group: 3.6 months) and the 1-year OS rate was 36%, as shown in Figure 2. Median follow-up was 5.2 (interquartile range 1.3–15.1) months. Among the 44 patients who died during follow-up, two died in CR of infectious complications. The other deaths occurred in patients with progressive disease. The causes of death were disease progression ($n=32$), infections ($n=11$) and acute GvHD ($n=1$). Among the 19 patients who were alive at last follow-up (median follow-up: 20.1 months), 6 had received DLI and 10 had developed chronic GvHD.

In univariable analysis, only the time from transplant to relapse was predictive of OS (hazards ratio: 0.33 (0.17–0.64), $P=0.0009$) (Table 3). Median OS was 2.7 months among patients with early post transplant relapse (<3 months) and 23.3 months in the other patients ($P=0.0009$). Age, disease status at transplantation, the type of conditioning regimen (RIC vs myeloablative-conditioning regimen), the relapse type (skin vs systemic), chronic GvHD and DLI were not associated with OS in a time-dependent analysis. In multivariate analysis, no factor was significant, except for the time from transplant to relapse.

Multivariable analysis identified two factors influencing the response to post-relapse treatment, namely chronic GvHD

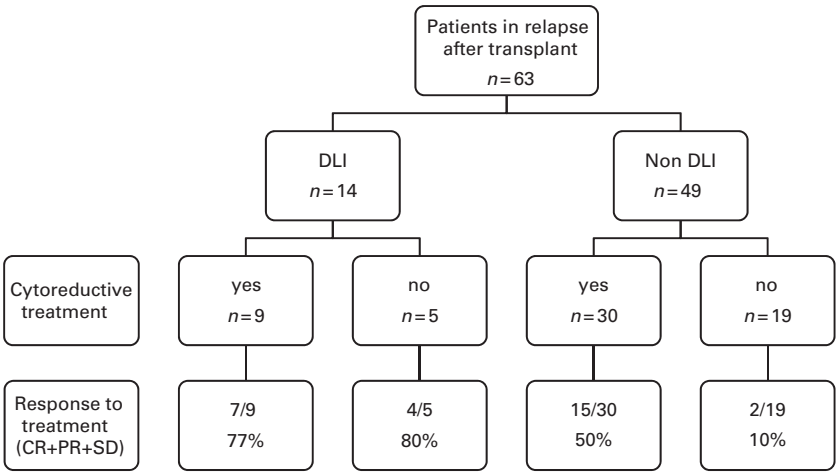

Figure 1. Treatments at post-transplant relapse and disease response to treatment in DLI and non-DLI group. This flowchart resumes the treatments, which were given at post-transplant relapse for the 63 patients, and the response observed, whereas they had received DLI or not, cytoreductive treatment (chemotherapy, radiation) or not. DLI = donor lymphocytes infusion; s.d. = stable disease.

Table 2. Outcome in the DLI group

Pts	*Age*	*Histologic subtype*	*CD*	*Donor*	*Type of relapse*	*Time allo-relapse (mths)*	*DLI (n)*	*Chronic GVHd after DLI*	*Associated treatment*	*Response to treatment*	*Survey after relapse (mths)*
1	16	ALCL ALK–	TBI EDX	Sibling 10/10	Cutaneous	6	2	No	Ø	CR	140.1
2	32	ATL	TBI EDX	UR 10/10	Nodes	17.3	1	Yes	CT	CR	33.7
3	53	ALCL ALK –	FB1	Sibling 10/10	Cutaneous	0.9	1	No	CT	PR	6.4
4	55	ALCL ALK+	FB2	Sibling 10/10	Nodes	4.6	1	No	Ø	s.d.	4.5
5	61	TCL NOS	FB3	UR 10/10	Cutaneous +nodes	18.7	3	No	RT	CR	10.5
6	17	MF	TBI EDX	UR 10/10	Cutaneous	16.8	1	Yes	Interféron alpha	CR	70.7
7	39	MF	FB3	Sibling 10/10	Cutaneous +nodes	3.5	1	Yes	Ø	CR	40.4
8	31	SS	FB2	UR 9/10	Cutaneous +blood	3.2	1	Yes	Ø	PR	23.6
9	44	NK/T NHL	FB3	Sibling 10/10	Nodes	6.6	2	No	CT	s.d.	7.4
10	41	TCL NOS	FLUDA TBI	Sibling 10/10	NA	13.3	1	Yes	RT	CR	76.5
11	62	TCL NOS	FB2	UR 10/10	Nodes	3.5	1	No	CT	PD	6.2
12	39	NK/T nasal	NA (MAC)	UR 9/10	NA	1.5	1	No	Ø	PD	11.8
13	55	TCL NOS	FB2	Sibling 10/10	Cutaneous	1.9	2	No	Bortezomib	CR	56.7
14	63	TCL NOS	FLUDA TBI	Sibling 10/10	Blood	1.6	1	No	CT	PD	5.5

Abbreviations: aGvH = acute graft versus host disease; ALCL = anaplastic large-cell lymphoma; ALK = anaplastic lymphoma kinase; B = busulfan; CD = conditioning regiment; cGvHd = chronic graft versus host disease; CR = complete response; CT = chemotherapy; DLI = donor lymphocyte infusion; EDX = endoxan; F = fludarabine; MAC = myeloablative regimen; MF = mycosis fungoide; mths = months; n = number; NA = non-available data; PD = progressive disease; PR = partial response; RT = radiotherapy; s.d. = stable disease; SS = Sézary syndrome; T NHL NOS = T-cell non-Hodgkin lymphoma 'not otherwise specified'; UR = unrelated.

(odds ratio: 11.25 (2.68–48.21), $P = 0.0009$) and isolated cutaneous relapse (odds ratio 4.15 (1.04–16.50), $P = 0.043$) (Tables 4 and 5).

DISCUSSION

Standard therapeutic strategies have given poor results in patients with PTCL. In addition to a high rate of primary chemo-refractory disease, the relapse rate reaches 40% after conventional chemotherapy with the CHOP regimen.[1] Conventional salvage therapies are also poorly effective, even if new molecules currently under investigation seem to be promising. The relapse rate after allo-SCT ranges from 15% to 49%, which is comparable to that seen after auto-SCT. However, some data suggest a beneficial allogeneic effect against PTCL. In a study by Dodero *et al.*,[5] 52 patients received second-line allografts with RIC. The OS rate among patients with chemoresistant disease before the graft was 29% at 5 years, suggesting a persistent GvL effect. Factors associated with an increased risk of relapse in the main studies, albeit in a limited number of patients, were the RIC regimen, T-cell depletion and chemoresistant disease before allo-SCT. Some authors also found a lower rate of relapse for cutaneous TCL.[17]

Tapering of immunosuppressive therapy is usually the first strategy after post transplant relapse. In our study, this was effective in two patients who developed chronic GvHD, in whom prolonged disease control was obtained without any other salvage treatment. Three similar cases of CR from PTCL after withdrawal of immunosuppressive drugs have been reported.[13,18,19]

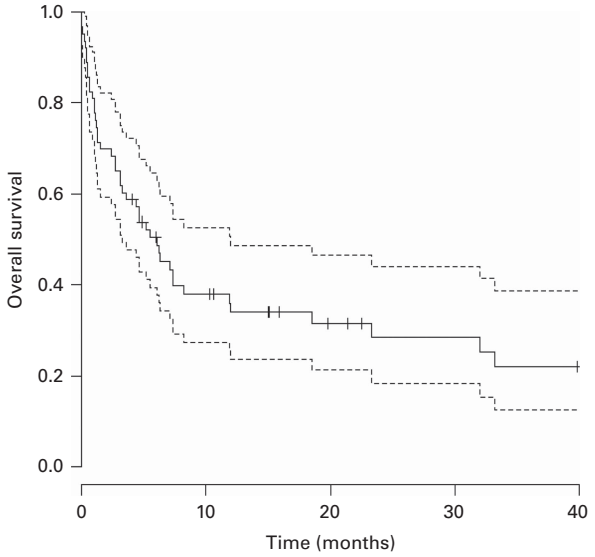

Figure 2. Overall survival estimation after post-transplant PTCL relapse in the 63 patients. This figure shows overall survival after post-transplant relapse in the 63 patients. Dotted lines represent interquartile range (25–75). Median follow-up is 5.3 (1.3–15.1) months. Median survival is 6.1 months and 1-year OS is 36% (CI 95%: 25.5–50.6).

Table 3. Univariate analysis of OS

	HR (95% CI)	P-*value*
DLI		
Yes	0.58 (0.24–1.44)	0.24
Gender		
Female	0.99 (0.51–1.95)	0.99
Age at relapse	1.02 (0.99–1.04)	0.15
Time from diagnosis to transplant		
> 1 year	0.85 (0.47–1.56)	0.61
Disease status at transplant		
CR	1	
PR	1.01 (0.52–1.94)	0.99
PD	0.73 (0.29–1.85)	0.5
Conditioning regimen		
MAC (vs RIC)	1.07 (0.57–2.01)	0.84
cGvHD		
Yes	0.42 (0.16–1.1)	0.075
Time from transplant to relapse		
>3 months	0.33 (0.17–0.64)	0.0009
Skin relapse		
Yes	1.4 (0.69–2.83)	0.35

Abbreviations: CR = complete response; cGvHd = chronic graft versus host disease; DLI = donor lymphocyte infusion; MAC = myeloablative regimen; RIC = reduced-intensity regimen; HR = hazard ratio; PD = progressive disease; PR = partial response.

DLI was considered as a therapeutic option by the clinicians managing 22% of the relapsing patients in our study. DLI is already approved as an effective strategy for other lymphoid malignancies in relapse after allo-SCT, such as low-grade B-cell lymphoproliferation.[20,21] In contrast, because of more rapid relapse, an immune strategy based on DLI is less effective in more aggressive diseases such as acute leukemia and large B-cell NHL. In the largest series of patients treated with DLI for cutaneous T-cell lymphoma, preceded by chemotherapy or radiotherapy for 5 of 12 patients, a response was observed in 8 patients.[5] A response to DLI has also been reported in a small number of patients with non cutaneous TCL.[4–6,8] Itonaga *et al.*[13] recently reported results for 35 patients who relapsed after allo-SCT for adult T-cell leukemia/lymphoma. Immunosuppressive drugs were tapered in 29 patients, resulting in two CRs. Nine patients received both cytoreductive therapy and DLI, leading to disease control in four cases, including three long-lasting responses, all associated with chronic GvHD. In this latter study the 3-year OS rate after relapse was 19.3%, which is encouraging in such an aggressive disease. The authors observed a better response to immune modulation preceded by chemotherapy.

Table 4. Univariate analysis of the response to treatment

	OR (95% CI)	P-*value*
Gender		
Female	0.74 (0.25–2.2)	0.58
Age at relapse	0.96 (0.92–1)	0.056
Number of previous therapy		
>1	3.75 (0.42–33.4)	0.24
Previous auto-SCT		
Yes	0.41 (0.1–1.69)	0.41
Time from diagnosis to allo-SCT		
>1 year	1.03 (0.32–3.334)	0.95
Disease status at transplant		
CR	1	
PR	1.00 (0.31–3.21)	1
PD	2.8 (0.67–11.67)	0.16
Conditioning regimen		
MAC (vs RIC)	0.7 (0.25–2)	0.51
cGvHD		
Yes	9.52 (2.75–32.9)	0.0004
Time from transplant to relapse	1.02 (0.97–1.07)	0.48
Immunosupressive drug at relapse		
Yes	1.45 (0.48–4.41)	0.51
Skin-isolated relapse		
Yes	3.64 (1.10–11.97)	0.034

Abbreviations: auto-SCT = autologous stem cell transplantation; allo-SCT = allogeneic stem cell transplantation; CR = complete response; cGvHd = chronic Graft versus Host disease; MAC = myeloablative regimen; OR = odd ratio; PD = progressive disease; PR = partial response.

Table 5. Multivariable analysis of the response to treatment

		OR (95% CI)	P-*value*
cGVHd	Yes	11.25 (2.68–48.21)	0.0009
Skin-isolated relapse	Yes	4.15 (1.04–16.50)	0.043

Abbreviation: cGvHd = chronic graft versus host disease.

In our study the treatments received before or together with DLI were very heterogeneous. Some patients received drugs known to interfere with immune responses prior to DLI, namely fludarabine, lenalidomide and interferon-alpha. Such drugs could have a more-targeted effect and lesser bone marrow toxicity than conventional chemotherapies, especially in the early post-transplant setting. Despite a small number of three patients who received brentuximab (one ALCL ALK+ and two T-NOS), we notice a long-lasting CR for all of them. These limited data, taken together with recent reports,[22] are promising.

We found that the main factor influencing OS was a longer time between transplant and relapse, reflecting both the disease burden but also the difficulty of choosing an appropriate and feasible post-relapse treatment. Another argument for a graft-versus-PTCL effect is the association between the onset of chronic GvHD and the response to treatment in multivariate analysis. This is in keeping with Dodero's study[5] where the relapse rate was 17% in patients with chronic GvHD and 66% in the absence of chronic GvHD ($P = 0.05$).

The comparative impact of immune modulation in the different histological subtypes is unclear. Although successful DLI has mainly been reported in primary cutaneous lymphoma, 8 of our 11 patients who responded to DLI had non cutaneous TCL. Moreover, the histological type was not a prognostic factor for OS. Among our 63 patients, 17 had isolated cutaneous relapse. This characteristic was associated with a better response to treatment. Indeed, all four patients who received DLI for isolated cutaneous relapse responded (one mycosis fungoide, two ALCL and one T-cell 'not otherwise specified').

Even if this cohort is the largest to date, the main limitation of this work is the heterogeneity of the study population. Indeed, whereas the two groups (DLI and non-DLI) were comparable for pre-transplant characteristics, we cannot assume that this was still true at the time of relapse. Obviously, for example, a patient who relapses with an aggressive and high-burden presentation is not a good candidate for immune modulation without associated treatment. To reduce this bias, we used statistical methods; in multivariate analysis of the prognostic impact of DLI and chronic GvHD, both factors were considered as time-dependent variable. Using this method, the impact of DLI on OS was NS, although OS was better for patients in DLI − group.

CONCLUSION

This series of 63 patients with post-allograft relapse of PTCL is the largest reported to date. It confirms the globally poor prognosis of patients with early relapse after allo-SCT. However, DLI, sometimes combined with cytoreductive treatment, led to prolonged responses, especially in patients with relatively indolent relapse. The only factor positively affecting OS was a longer time from transplant to relapse. Factors predictive of a better response to treatment at relapse were skin isolated relapse and chronic GvHD.

The study population was heterogeneous and included patients with primary cutaneous TCL. Relapse occurred early after transplantation, hindering the use of immune strategies. In addition, the choice of treatment at relapse was left to the individual clinician, according to local procedures. Patients who received DLI might have been those who were able to receive this treatment because their general condition was better, because the disease was not completely uncontrolled at the time of DLI, or because the relapse did not occur too early after transplantation. In the statistical estimation of OS, DLI and cGvHD were included as time-dependent variables to avoid this bias. Four patients had prolonged responses after DLI alone or after immunosuppressive drug tapering alone, who were followed by chronic GvHD. This suggests the existence of a true GvL effect in PTCL. We believe that immune modulation should be a part of the therapeutic strategy, when feasible, for PTCL patients who relapse after allo-SCT. In future, a preventive immune modulation strategy prior to relapse might be an option for high-risk patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ACM[1] and SN[20] designed the study and wrote the paper; VL[2] and MB[2] performed the statistical analysis, VL[2] and MB[2] contributed to the analysis of the results, PC, DB, SV, AX, NF, NC, YB, NI, CEB, FS, IYA, PT, ED, TL, JYC, AH, SM, KB, MO, JOB, GG, NM, MM, TD, JHB, FR, RO, CJ contributed to the data collection.

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