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ORIGINAL ARTICLE

Prognostic factors for donor lymphocyte infusions following non-myeloablative allogeneic stem cell transplantation in multiple myeloma

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In this retrospective study, we evaluated donor lymphocyte infusions given for relapsed ($n = 48$) or persistent ($n = 15$) myeloma following non-myeloablative allogeneic stem cell transplantation (Allo-SCT). Twenty-four of 63 patients (38.1%) responded: 12 patients (19.0%) with a partial response (PR) and 12 patients (19.0%) with a complete response (CR). Overall survival after donor lymphocyte infusions (DLI) was 23.6 months (1.0–50.7+). Median overall survival for non-responding patients was 23.6 months and has not been reached for the patients responding to DLI. In responders, progression-free survival after DLI was 27.8 months (1.2–46.2+). Patients with a PR had a median progression-free survival of 7.0 months, whereas patients with a CR to DLI had a median progression-free survival of 27.8 months. Major toxicities were acute graft-versus-host disease (GVHD) (38.1%) and chronic GVHD (42.9%). Seven patients (11.1%) died from treatment-related mortality. The only significant prognostic factors for response to DLI were the occurrence of acute and chronic GVHD. There was a trend towards significance for time between transplantation and DLI, and response. Donor lymphocyte infusion following non-myeloablative Allo-SCT is a valuable strategy for relapsed or persistent disease.

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Keywords: donor lymphocyte infusion; non-myeloablative allogeneic stem cell transplantation; multiple myeloma; prognostic factors

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Introduction

In myeloma, allogeneic stem cell transplantation (Allo-SCT) is associated with a longer progression-free survival in comparison to autologous-SCT.[1] This is probably owing to the graft-versus-myeloma (GVM) effect mediated by immune competent donor lymphocytes.[2] Unfortunately, myeloablative Allo-SCT is associated with a high transplant-related mortality, ranging between 30 and 50% in published studies.[3–5] Non-myeloablative conditioning can establish durable and stable engraftment with acceptable transplant-related mortality and excellent disease control in various hematological malignancies including multiple myeloma.[6–8]

Donor lymphocyte infusions (DLI) given for relapsed myeloma following myeloablative Allo-SCT induce response rates in 30–50% of patients.[9–13] A recent study showed that DLI is a potential treatment strategy for myeloma patients with relapse after non-myeloablative Allo-SCT.[14] In this retrospective study, we analyzed the efficacy, toxicity and prognostic factors for response to DLI following non-myeloablative Allo-SCT in a larger group of myeloma patients.

Study design

Donor lymphocyte infusions

Eight European transplantation centers participated in this study. Patients who were refractory to or who experienced relapse after non-myeloablative Allo-SCT were candidates for DLI. Patients with World Health Organization (WHO) performance status of 4, active graft-versus-host disease (GVHD), severe infection and abnormal liver and renal function were ineligible for the study (creatinine $>180\,\mu$mol/l, bilirubin twice the normal value). A total of 63 patients

were included. If there was no response to DLI and no signs of GVHD after a minimum observation period of 3 months, patients could receive a second course of DLI with a higher T-cell dose. A further dose escalation could be performed in the event of no response/GVHD following this second DLI. No prophylactic immunosuppression was prescribed following DLI. Treatment of acute and chronic GVHD was performed according to local protocols. Approval was obtained from the institutional review board of the participating centers. Written informed consent was obtained from all patients before inclusion. The study was performed according to the Helsinki agreement.

Definitions

Response to reinduction therapy, to DLI and salvage therapy was assessed according to the criteria of the European Group for Blood and Marrow Transplantation (EBMT).[15] Overall survival was measured in months and defined from the date of DLI to the date of death or last follow-up. Progression-free survival was defined as the time from DLI to date of progression or death from any cause or last follow-up. Acute GVHD was grade I–IV according to the Seattle criteria[16] and chronic GVHD was defined as limited or extensive according to Shulman *et al*.[17] Treatment-related mortality was defined as death owing to any cause other than disease progression or relapse occurring at any time after transplant. When patients received DLI in partial response (PR), they were considered to have low tumor load. High-risk myeloma was defined by the presence of chromosome 13 deletion (fluorescent *in situ* hybridisation) and/or a β2-microglobulin > 3 mg/l at diagnosis.

Chimerism analysis

Chimerism analysis was performed according to each institution's standard practice guidelines.

Statistical analysis

Overall survival, progression-free survival and treatment-related mortality were estimated by the Kaplan–Meier method. Univariate Cox regression analysis was used to determine the prognostic value for overall and progression-free survival. The Mann–Whitney *U*-test was used to determine differences in continuous variables between patients who responded to DLI and patients who did not. Differences in categorial variables were determined with the Fisher's exact test for two by two tables and otherwise with the Pearson's χ^2-test. Calculations were performed in SPSS version 12.0.1 (SPSS Inc., IL, USA).

Results

Patient characteristics

Donor lymphocyte infusions were administered after non-myeloablative Allo-SCT for treatment of relapse in 48 patients or persistent disease in 15 patients. Median age was 54.5 years (range, 36.1–70.4) (Table 1). Fifty-eight patients underwent non-myeloablative Allo-SCT with preceding autologous SCT, and five patients had no preceding autologous SCT before the non-myeloablative Allo-SCT. In 23 patients, non-myeloablative Allo-SCT was part of first-line treatment. Fourteen patients were conditioned with low-dose total body irradiation (TBI; 2 Gy) and fludarabine (90 mg/m^2) and eight patients with TBI only;[8] 41 patients were conditioned with a semi-intensive conditioning regimen including melphalan 100–140 mg/m^2[18,19] in 21 or thiotepa and cyclophosphamide in 20 patients.[20] Forty-six patients had a sibling donor and 17 had a matched unrelated donor. Thirty patients received an unmanipulated full graft and 33 patients a partially (*in vivo*) T-cell-depleted graft (ATG/alemtuzumab). Eighteen patients (28.6%) experienced acute GVHD grade I–IV and 10 patients (15.9%) chronic GVHD before DLI. Twelve patients received reinduction therapy (VAD based) before administration of DLI. A total of 92 courses of DLI have been administered (range, 1–4 courses). The median time interval between stem cell transplantation and DLI was 7.6 months (range, 3.0–34.5 months). T-cell dose of DLI varied between 1×10^6 and 3×10^8 T-cells/kg. In the vast majority of the patients, the starting dose was $< 1 \times 10^7$ T-cells/kg.

Table 1 Patient characteristics ($N = 63$)

	No. of patients
Age (years)	
Median	54.5
Range	36.1–70.4
Sex	
Male	36
Female	27
Conditioning regimen NMA	
TBI	8
TBI and fludarabine	14
Melphalan (100–140 mg/m^2)	21
Thiotepa and cyclophosphamide	20
Previous autologous SCT	
No	5
Yes	58
Extent of prior therapy	
NMA as part of first-line treatment	23
NMA not part of first-line treatment	40
Stem cell source	
Sib	46
MUD	17
Transplant graft	
T-cell depleted	33
Non-T-cell depleted	30

Abbreviations: NMA = non-myeloablative Allo-SCT; MUD = matched unrelated donor; Sib = sibling donor; TBI = total body irradiation.

Outcome of donor lymphocyte infusions

Twelve patients (19.0%) achieved a PR and 12 patients (19.0%) a complete response (CR), resulting in a total response rate to DLI of 38.1% of patients. In seven patients, response was induced after dose escalation. Four patients responded after two courses, two after three

courses and one after four courses. In the remaining patients, response was seen after the first DLI. The median follow-up time after DLI of the 43 (68.3%) patients still alive was 14.0 months (range, 3.0–50.7). Nine patients relapsed from DLI, five from PR and four from CR. Twenty patients (31.7%) have died, 13 (20.6%) from progressive disease and seven (11.1%) from treatment-related mortality.

Median progression-free survival for all responding patients after DLI was 27.8 months (range, 1.2–46.2+) (Figure 1a). Patients with a PR had a median progression-free survival of 7.0 months, whereas patients with a CR to DLI had a median progression-free survival of 27.8 months (Figure 1b). Median overall survival of the whole group of patients was 23.6 months (range, 1.0–50.7+) (Figure 2a). Median overall survival for non-responding patients was 23.6 months and has not been reached for the patients responding to DLI (Figure 2b).

Toxicity

Seven patients (11.1%) have died from treatment-related mortality. Five patients died of GVHD, one patient from

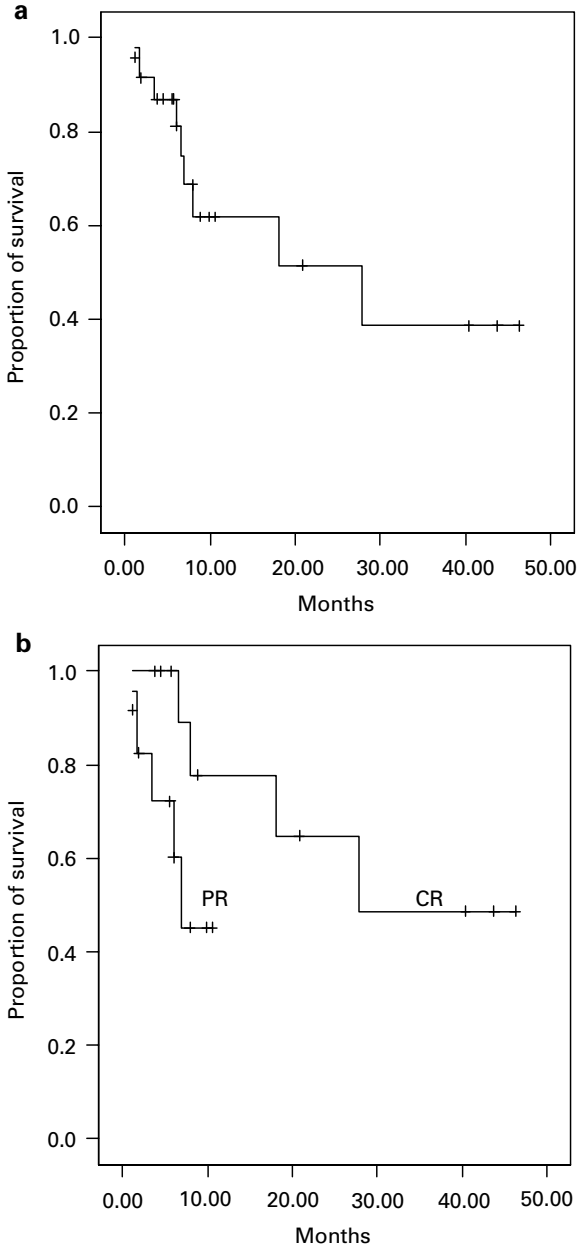

Figure 1 Progression-free survival. Progression-free survival following donor lymphocyte infusions after non-myeloablative allogeneic stem cell transplantation: (**a**) whole group; (**b**) for patients who achieved a partial response (PR) and complete response (CR).

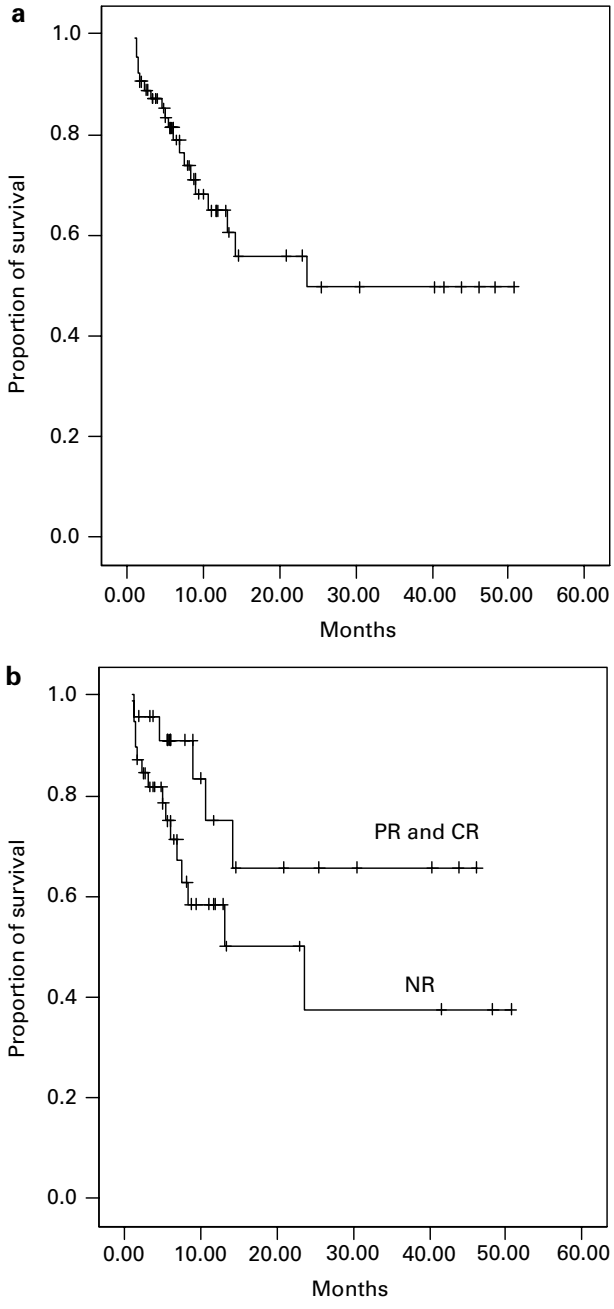

Figure 2 Overall survival. Overall survival following donor lymphocyte infusions after non-myeloablative allogeneic stem cell transplantation: (**a**) whole group; (**b**) for responding (PR and CR) and non-responding patients (NR).

interstitial pneumonitis and one patient from a massive lung embolus during thalidomide therapy. Treatment-related mortality at 100 days and at 1 year was 5.0 and 17.2%, respectively (Figure 3). In univariate Cox regression analysis, previous T-cell depletion with non-myeloablative transplantation was associated with a lower DLI treatment-related mortality in comparison with an unmanipulated full graft ($P=0.030$) (Table 2). Acute GVHD following DLI resulted in a higher treatment-related mortality with borderline significance ($P=0.100$) (Table 2). Acute GVHD following DLI occurred in 24 patients (38.1%): grade 1 in 10 (15.9%), grade 2 in four (6.3%), grade 3 in eight (12.7%) and grade 4 in two patients (3.2%). Chronic GVHD following DLI occurred in 27 patients (42.9%): 21 patients (33.3%) with limited and six patients (9.5%) with extensive GVHD. The occurrence of chronic GVHD did not influence treatment-related mortality. All other factors tested were not predictive for treatment-related mortality (Table 2). There was no correlation between prior acute or chronic GVHD and the development of acute or chronic GVHD following DLI. The incidence of acute or chronic GVHD after DLI was not higher in unrelated donors and was not affected by T-cell dose. The conditioning regimen and T-cell depletion were not associated with acute GVHD after DLI. However, the occurrence of chronic GVHD after DLI was significantly higher in patients who received a semi-intensive conditioning regimen (53.7 versus 22.7%; $P=0.032$) or a partially T-cell-depleted graft (57.6 versus 26.7%; $P=0.021$), compared to patients who were conditioned with low-dose TBI and fludarabine or who received an unmanipulated full graft, respectively.

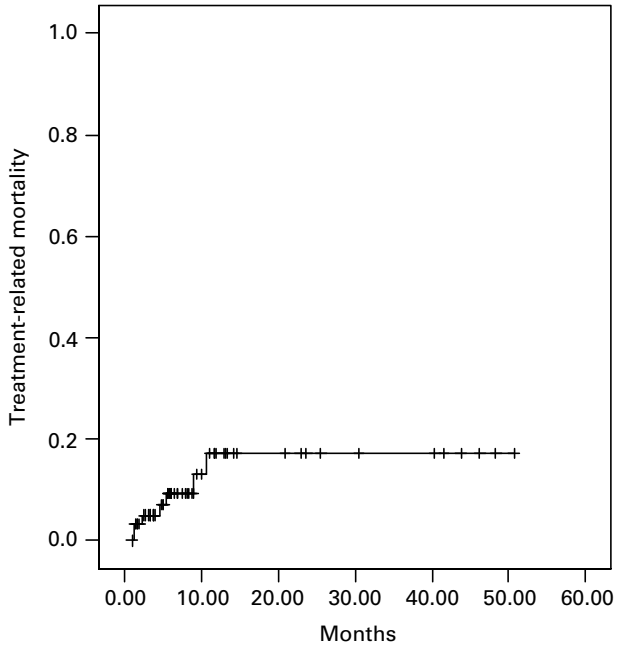

Figure 3 Treatment-related mortality. Treatment-related mortality following donor lymphocyte infusions after non-myeloablative allogeneic stem cell transplantation.

Predictive factors for response and survival

In univariate analysis, only acute GVHD ($P<0.001$) and chronic GVHD ($P=0.001$) were significantly associated with response to DLI (Table 3). Response to DLI was 66.7% in patients with acute GVHD and 63.0% in patients with chronic GVHD, whereas only 20.5% of the patients without acute GVHD and 19.4% of the patients without chronic GVHD responded to DLI. Only four of the 63 patients obtained a response without any signs of acute and chronic GVHD (4 PR). Median progression-free survival was 7.0 months for patients without acute and chronic GVHD and 27.8 months for patients with acute or chronic GVHD ($P=0.329$). There was a trend towards significance for time between transplantation and DLI, and the response to DLI ($P=0.062$). Response to DLI was 55.0, 36.4 and 23.8% in patients who received their DLI within 6 months, between 6 and 12 months and after 12 months following Allo-SCT, respectively. All other

Table 2 Predictive factors for OS, PFS and TRM, univariate analysis

Characteristic	*OS;* P	*PFS;* P	*TRM;* P
Age	0.258	0.041	0.389
Sex	0.307	0.493	0.822
Time interval between previous Tx and DLI	0.109	0.306	0.106
Acute GVHD after previous Tx	0.270	0.285	0.321
Chronic GVHD after previous Tx	0.601	0.102	0.916
Conditioning regimen non-myeloablative Allo-SCT	0.969	0.661	0.192
T-cell depletion (ATG/anti-CD52)	0.465	0.462	0.030
Reinduction therapy	0.942	0.602	0.570
T-cell dose of DLI	0.807	0.582	0.809
Chimerism of peripheral blood cells at the time of DLI, T/non-T[a]	0.114	0.691	0.919
Stem cell source	0.085	0.783	0.458
Acute GVHD I–IV following DLI	0.504	0.267	0.100
Chronic GVHD following DLI	0.207	0.065	0.924
High risk[b]	0.148	0.445	0.587
Response DLI	0.019	0.060	0.287

Abbreviations: DLI = donor lymphocyte infusion; GVHD = graft-versus-host disease; OS = overall survival; PFS = progression-free survival; TRM = treatment-related mortality; Tx = transplantation.
[a]Determined in 56 patients (88.9%).
[b]Determined in 41 patients (65.1%).

Table 3 Predictive factors for response to DLI, univariate analysis

Characteristic	*Total no. of patients*	*No. of patients with response (%)*	P
Age (years)			
<55	31	11 (35.5)	0.977
>55	32	13 (40.6)	
Sex			
Male	36	14 (38.9)	1.000
Female	27	10 (37.0)	
Time interval between previous Tx and DLI (months)			
<6	20	11 (55.0)	0.062
6–12	22	8 (36.4)	
>12	21	5 (23.8)	
Acute GVHD after previous Tx			
Grade 0–I	45	17 (37.8)	1.000
Grade II–IV	18	7 (38.9)	
Chronic GVHD after previous Tx			
No	53	19 (35.8)	0.485
Yes	10	5 (50.0)	
Conditioning regimen NMA			
Low-dose TBI	22	6 (27.3)	0.278
Semi-intensive	41	18 (43.9)	
Previous autologous SCT			
No	5	3 (60.0)	0.360
Yes	58	21 (36.2)	
Extent of prior therapy			
NMA as part of first-line treatment	23	8 (34.8)	0.790
NMA not part of first-line treatment	40	16 (40.0)	
T-cell depletion (ATG/anti-CD52)			
No	30	9 (30.0)	0.299
Yes	33	15 (45.5)	
Reinduction therapy			
No	51	21 (41.2)	0.345
Yes	12	3 (25.0)	
Response to reinduction therapy			
No	6	1 (16.7)	1.000
Yes	6	2 (33.3)	
LDH at the time of DLI[a]			
Normal	48	19 (39.6)	0.638
Elevated	5	3 (60.0)	
DLI reason			
Relapse	48	20 (41.7)	0.371
Persistent disease	15	4 (26.7)	
Tumor load			
High	42	18 (42.9)	0.410
Low	21	6 (28.6)	
T-cell dose of DLI			
$<1\times10^7$	34	13 (38.2)	1.000
$\geqslant1\times10^7$	29	11 (37.9)	
Chimerism of peripheral blood cells at the time of DLI, T/non-T[b]			
Donor	47	17 (36.2)	0.715
Mixed	9	4 (44.4)	
Stem cell source			
Sibling	46	18 (39.1)	0.765
Matched unrelated donor	17	6 (35.3)	
Acute GVHD following DLI			
No	39	8 (20.5)	<0.001
Grade I–IV	24	16 (66.7)	
Chronic GVHD following DLI			
No	36	7 (19.4)	0.001
Yes	27	17 (63.0)	
High risk[c]			
No	20	6 (30.0)	0.744
Yes	21	8 (38.1)	

Abbreviations: DLI = donor lymphocyte infusion; GVHD = graft-versus-host disease; NMA = non-myeloablative Allo-SCT; SCT = stem cell transplantation; TBI = total body irradiation; Tx = transplantation.
The Mann–Whitney *U*-test was used to compare good and poor responders with respect to continuous variables. Differences in categorial variables were determined with the Fisher's exact test for two by two tables and otherwise with the Pearson's χ^2 test.
When patients received DLI in PR, they were considered to have low tumor load.
[a]Determined in 53 patients (84.1%).
[b]Determined in 56 patients (88.9%)
[c]Determined in 41 patients (65.1%).

factors tested including age, sex, acute GVHD after Allo-SCT, chronic GVHD after Allo-SCT, conditioning regimen, previous autologous SCT, extent of prior therapy, T-cell depletion, reinduction therapy before DLI, response to reinduction therapy, LDH at the time of DLI, T-cell dose of DLI, DLI reason including relapse or persistent disease, tumor load, chimerism of peripheral blood cells at the time of DLI, high-risk myeloma or stem cell source were not predictive (Table 3). Two patients had extramedullary relapse combined with systemic relapse. In one patient with a single skin plasmacytoma, DLI was preceded by local radiotherapy, which resulted in complete disappearance of the plasmacytoma. This patient responded to DLI with a PR. The other patient had multiple soft tissue plasmacytomas and was refractory to DLI. Multivariate analysis showed that both acute GVHD ($P=0.012$) and chronic GVHD ($P=0.021$) were independent predictive factors for response to DLI.

Univariate Cox regression analysis showed that overall survival was significantly longer in patients responding to DLI, when compared to non-responding patients ($P=0.019$). Achieving CR to DLI resulted in a longer progression-free survival with borderline significance, when compared to achieving PR ($P=0.060$). All other variables tested were not predictive for overall and progression-free survival (Table 2).

Salvage therapy

Sixteen patients not responding to DLI and two patients relapsing after DLI were treated with bortezomib and/or

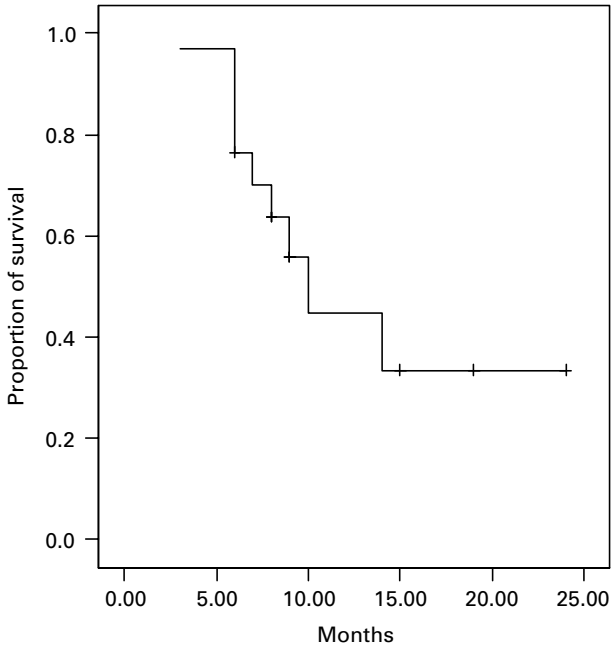

Figure 4 Progression-free survival following bortezomib or thalidomide salvage therapy.

thalidomide. Fifteen of these 18 patients (83.3%) responded including all seven patients treated with bortezomib and six of nine patients treated with thalidomide. Two patients receiving both drugs achieved a CR, which are still ongoing for 8 and 19 months. Median progression-free survival following bortezomib or thalidomide salvage therapy was 10.0 months (Figure 4).

Discussion

This study shows that DLI following non-myeloablative Allo-SCT is a valuable strategy for relapsed or persistent disease. Although major drawbacks remain that the GVM effect of DLI seems inextricably bound up with the occurrence of GVHD and durable remissions are restricted to a minority of patients who achieve CR. Major toxicity was as expected GVHD, which had a higher incidence following T-cell depletion. However, this did not translate into a higher treatment-related mortality.

The dissociation of GVHD and GVM is of vital importance in improving the efficacy of Allo-SCT and DLI, while toxicity, that is GVHD, is reduced. High response rates were induced in patients with relapsed myeloma by combining DLI with thalidomide.[21] The low incidence of GVHD in this study was striking and suggests that the improvement of the GVM effect was not associated with stimulation of GVHD. Several other *in vivo* and *in vitro* studies have shown that novel agents effective against myeloma like bortezomib, thalidomide and its derivates may have strong immune modulating effects that could result in enhancement of graft-versus-tumor reactions without stimulation of GVHD.[22,23] In our study population, survival after DLI was remarkably long, probably also owing to the fact that 15 of 18 patients (83.3%) not responding to ($n=16$) or relapsing after DLI ($n=2$) were sensitive to salvage therapy with novel agents bortezomib and thalidomide. In two patients, response was preceded by a transitory flare up of GVHD grade 1 (one skin, one skin and liver; the skin GVHD was histologically proven), suggesting that immune modulation contributed to the response.[24]

Several conclusions can be made from our observations, with the restriction that this is a retrospective study in a relatively small group of patients conditioned with multiple preparative regimens and treated with DLI with a highly variable T-cell number. The first one is that the picture of DLI in the non-myeloablative setting (response and prognostic factors) is not different from that observed in conventional Allo-SCT. However, other prognostic factors may be identified when a larger homogeneously treated group of patients will be analyzed. The second one is that the approach to the patient with relapse or persistent disease after Allo-SCT should be changed. Given the remarkable activity of the novel agents in this setting and given the fact that immunotherapy is most effective in the setting of minimal residual disease, it would be rational to maximally cytoreduce patients with these novel agents before DLI and continue treatment following DLI to try to stimulate GVM without GVHD. These new strategies might also include the application of maintenance treatment with novel agents immediately following non-myeloablative Allo-SCT, eventually combined with low-dose DLI in the case that CR is not achieved. In such studies, GVHD and GVM should be monitored closely in relation with *in vivo* immunoreactivity (i.e. effects on cellular subsets and cytokines).

In conclusion, the effectiveness of DLI following non-myeloablative Allo-SCT in myeloma was confirmed in this retrospective study. It is however questionable whether DLI as a single treatment should be the first option for patients with relapsed or persistent disease. Prospective studies are warranted in which novel agents like bortezomib, thalidomide and its derivates are explored in the treatment of relapsed and persistent disease following non-myeloablative Allo-SCT, alone or in combination with (low dose) DLI.

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