

Single-centre experience with nonmyeloablative allogeneic stem cell transplantation in patients with multiple myeloma: prolonged remissions induced

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ABSTRACT

Background: The role of allogeneic stem cell transplantation in multiple myeloma is not yet established.

Methods: We retrospectively evaluated the outcome of nonmyeloablative allogeneic stem cell transplantation (NMA) in patients with multiple myeloma treated at the Department of Haematology of the University Medical Centre Utrecht. Thirty-six patients received NMA as part of the first-line treatment; 23 patients as part of salvage therapy. Conditioning regimen was low-dose total body irradiation (TBI, 2 Grays) only; fludarabine was added in patients without previous autologous stem cell transplantation and patients with matched unrelated donors received antithymocyte globulin in addition to fludarabine and TBI.

Results: Following NMA overall response increased from 84 to 90%, complete remission rate from 15 to 32%. As part of first-line treatment NMA induced complete remission in 50% of patients vs one patient (4%) treated for relapsed multiple myeloma. Median progression-free survival was 26 months (13 months for the salvage group, 38 months for the 'upfront' patients). Median overall survival has not been reached yet. The achievement of complete remission following NMA as part of first-line treatment was associated with prolonged progression-free and overall survival. Major toxicities were acute and chronic graft-vs-host disease occurring in 64% (23% grade 3-4) and in 54% (49% extensive) patients, respectively. Seven patients (12%) died from nonrelapse mortality, five patients (9%) directly related to toxicity of NMA.

Conclusion: NMA in multiple myeloma is feasible, is associated with acceptable nonrelapse mortality and may

induce prolonged complete remission. In pretreated patients the result of NMA is disappointing which urges new strategies.

KEYWORDS

Myeloma, nonmyeloablative allogeneic stem cell transplantation

INTRODUCTION

Allogeneic stem cell transplantation (ASCT) is probably the only treatment with a curative potential for multiple myeloma. This is due to the graft-vs-myeloma effect, mediated by immune competent donor lymphocytes, best illustrated by the induction of sustained remissions following donor lymphocyte infusions after ASCT.¹⁻³ However, the necessity of performing ASCT in multiple myeloma is disputed as no survival advantage has been obtained compared with autologous SCT, in particular when myeloablative conditioning for the ASCT is applied.⁴ An important factor for this is the high nonrelapse mortality associated with myeloablative conditioning.^{4,5}

In an attempt to lower nonrelapse mortality and make ASCT available to more patients, nonmyeloablative conditioning was introduced. Nonmyeloablative ASCT (NMA) is associated with reduced acute toxicity, while antitumour activity is probably maintained.⁶⁻⁹ In this

retrospective single centre study we show that NMA is feasible in multiple myeloma, with acceptable nonrelapse mortality and that prolonged remissions may be induced in patients who received NMA as part of first-line treatment and achieved a complete remission following SCT.

PATIENTS AND METHODS

Selection of patients

Patients with multiple myeloma who received an NMA at the University Medical Centre Utrecht, the Netherlands, between September 2001 and September 2005 were included in this retrospective study. During this period, the human leucocyte antigens (HLA) class I (HLA-A, HLA-B, HLA-C) and class II (HLA-DR, HLA-DP, HLA-DQ) were typed in the first three months after diagnosis in all newly diagnosed patients younger than 66 years and their siblings. If an HLA-matched sibling donor was available (1 factor class I or class II mismatch was allowed), patients could proceed to NMA between two and six months after high-dose melphalan (HDM) 200 mg/m² and autologous stem cell rescue, which followed three courses of induction therapy with vincristine, adriamycin, dexamethasone (VAD) or thalidomide, adriamycin, dexamethasone (TAD).¹⁰ Also patients with a relapse after the preceding treatment but responsive to salvage therapy and with an HLA-matched related or unrelated donor were eligible for subsequent NMA.

Conditioning

The conditioning regimen before allogeneic stem infusion for the patients with completely matched HLA-identical sibling donors consisted of one course of low-dose total body irradiation (TBI) (2 Grays) only, if they had received HDM 200 mg/m² within the preceding two and six months (tandem auto-NMA). Fludarabine 30 mg/m² intravenously for three days was added if no preceding autologous SCT had been performed. The conditioning regimen before allogeneic stem infusion for the patients with an HLA-mismatched or unrelated donor consisted of antithymocyte globulin (ATG; 2 mg/kg/day for 4 days) followed by fludarabine 30 mg/m² intravenously for three days and one course of low-dose TBI (2 Grays).

Immunosuppression

In the post-transplantation period all patients were treated with the immunosuppressive drugs cyclosporine A (CSP) and mycophenolate mofetil (MMF). Patients received 30 mg/kg/day MMF for 60 to 90 days and 2 x 4.5 mg/kg/day CSP for three to six months according to the Seattle regimen.⁸

GVHD grading and treatment

For diagnosing and grading acute graft-vs-host disease (GvHD) the Gluckberg criteria¹⁰ were used. Chronic GvHD was graded according to the Seattle classification.¹¹ Time of onset of acute and chronic GvHD and grade of GvHD were monitored. Acute GvHD > grade I was treated with prednisone 1-2 mg/kg/day and when necessary topical prednisone treatment was applied. In these cases the doses of CSP and/or MMF were increased or continued. In case of steroid-refractory acute GvHD other drugs were used, such as sirolimus, tacrolimus, rituximab or more experimental drugs, such as alemtuzumab and dacluzimab.

Chronic GvHD of the skin was treated with topical prednisone. In severe cases of extensive chronic GvHD prednisone 1 mg/kg/day was given.

Definitions

Response and progression were determined according to the European Group for Blood and Marrow Transplantation (EBMT) criteria.¹² In short, a partial response was defined as ≥50% reduction of serum M-protein or ≥90% reduction in 24-hour excretion of Bence Jones proteinuria in case of light chain disease (LCD). A complete response was defined as complete disappearance of serum and urine M-protein as determined by immune fixation of serum and tenfold concentrated urine. In addition monoclonal myeloma cells as determined by immune phenotyping had to be absent in a representative bone marrow aspirate or biopsy. Nonrelapse mortality was defined as any death not related to progressive or relapsed myeloma.

Statistical analysis

For the statistical analysis SPSS 12.0.1 for Windows (SPSS Inc., IL, and USA) was used. Overall survival was measured in months and defined as the time from the date of transplantation until the date of death or last follow-up. Progression-free survival was measured in months and defined as the time from the date of transplantation until the date of progression or death from any cause or last follow-up. Time to acute or chronic GvHD was calculated from the date of transplantation until occurrence of acute or chronic GvHD.

Probabilities of overall survival, progression-free survival, and nonrelapse mortality were calculated using the Kaplan-Meier method. Kaplan-Meier curves were generated to illustrate survival and the log-rank test was used to compare survival curves between subgroups.

Univariate Cox regression analysis was used to determine the prognostic value of various variables for overall survival and progression-free survival. The predictive value of acute and chronic GvHD for overall and progression-free survival was calculated using a time-dependent univariate Cox regression analysis.

RESULTS

Patient characteristics

Fifty-nine patients were included in this study. The median age was 55 (range 35 to 67). There were 42 males (71%) and 17 females (28%). The median follow-up duration of survivors was 25.2 months (range 6.8 to 54.6) (table 1). In 36 patients (61%), NMA was part of first-line treatment and in 23 patients (39%) it was part of salvage treatment. At the time of transplant, nine patients (15%) were in complete remission and 40 patients (68%) were in partial remission.

Forty-four patients (74%) had a matched related donor, four patients (7%) had a partially matched related donor and six patients (10%) had a matched unrelated donor, and five patients (9%) had a partially matched unrelated donor. In 16 cases (27%) there was a female donor and a male recipient. Thirty-five patients (59%) were conditioned with TBI only (2 Gy) and 24 (41%) with TBI and fludarabine (30 mg/m²/day for 3 days).⁷ Fifteen patients (25%) received

ATG as *in vivo* T-cell depletion. At the time of diagnosis 21 out of 50 patients (42%) had chromosome 13 abnormalities in FISH analysis and 20 out of 44 patients (46%) had an elevated β_2 -microglobulin (≥ 3.0 mg/l).

Response and survival

Total response rate following NMA increased from 83% (n=49) to 92% (n=54); complete response rate increased from 15 to 32%. NMA as part of first-line treatment induced a complete remission in 50% of patients, as compared with achievement of a complete remission in one patient (4%) treated for relapsed multiple myeloma. An ongoing response, defined as improvement of partial to complete response and from no response to partial or complete response occurred in 24% of patients; 28% in patients who received NMA as part of first-line treatment and 17% in patients who received NMA as part of relapse treatment (table 2).

Twenty-five patients (42%) relapsed or progressed after NMA, two from complete remission and 23 from partial remission. At the time of analysis 48 patients were alive. Eleven patients (19%) had died, four from progressive disease and seven (12%) from nonrelapse mortality. The estimated overall survival of the whole group of patients at two years was 84% (figure 1). Median progression-free survival was 23.5 months (range 1.0 to 38.0 months; figure 2). In patients who received NMA as part of first-line therapy, overall and progression-free survival at two years were 88.9 and 68.9%, respectively (figures 3A and B). The achievement of complete remission after NMA in this group of patients was associated with superior overall survival and progression-free survival (figures 4A and B). Also the presence of complete remission before NMA was associated with prolonged progression-free survival (p=0.037), but not with prolonged overall survival (p=0.234). The occurrence of chronic GvHD was associated with prolonged overall

Table 1. Patient characteristics (n=59)

	No. of patients (%)
Sex	
Male	42 (71.2)
Female	17 (28.8)
Age (years)	
Median	55
Range	35-67
Median follow-up¹ (months)	
Median	25.2
Range	6.8-54.6
Extent of prior therapy	
First-line treatment	36 (61.0)
Relapse treatment	23 (39.0)
Donor	
MRD	44 (74.6)
PMRD	4 (6.8)
MUD	6 (10.2)
PMUD	5 (8.5)
Conditioning regimen	
TBI	35 (59.3)
TBI and fludarabine	24 (40.7)
Donor sex match	
Female to male	16 (27.1)
Other	43 (72.9)
Deletion of chromosome 13²	
Presence of deletion of chromosome 13	21 (42.0)
Absence of deletion of chromosome 13	29 (58.0)
β_2-microglobulin³	
<3 mg/l	24 (54.5)
>3 mg/l	20 (45.5)
Status at the time of ASCT	
CR	9 (15.3)
No CR	50 (84.7)

ASCT = allogeneic stem cell transplantation; CR = complete response; MRD = matched related donor; MUD = matched unrelated donor; PMRD = partially matched related donor; PMUD = partially matched unrelated donor; TBI = total body irradiation.

¹Follow-up duration of survivors; ²determined in 50 patients (84.7%); ³determined in 44 patients (74.6%).

Table 2. Response rates to nonmyeloablative ASCT in first-line and relapse treatment

	Total no. of patients (%)	First-line treatment n (%)	Relapse treatment n (%)	P
Remission state before ASCT				
CR	9 (15.3)	9 (25)	0 (0)	0.007
PR	40 (67.8)	24 (66.7)	16 (69.6)	
NR	10 (16.9)	3 (8.3)	7 (30.4)	
Remission state after ASCT				
CR	19 (32.2)	18 (50)	1 (4.3)	<0.001
PR	35 (59.3)	17 (47.2)	18 (78.3)	
NR	5 (8.5)	1 (2.8)	4 (17.4)	

ASCT = allogeneic stem cell transplantation; CR = complete response; PR = partial response; NR = no response. Differences in categorical variables were determined with the Pearson χ^2 test.

Figure 1. Overall survival following nonmyeloablative allogeneic stem cell transplantation

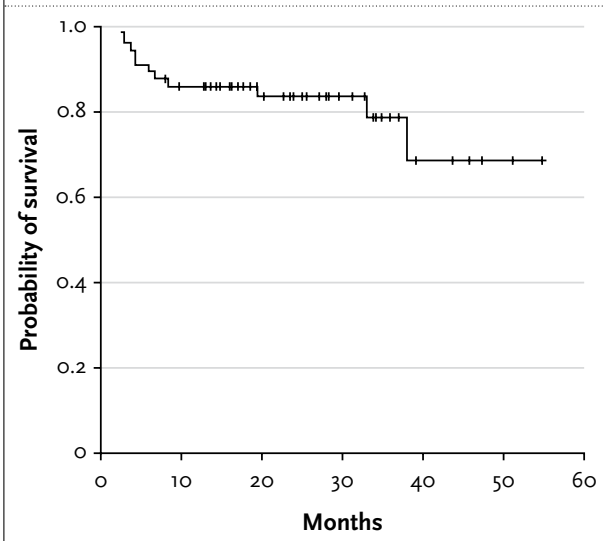


Figure 2. Progression-free survival following nonmyeloablative allogeneic stem cell transplantation

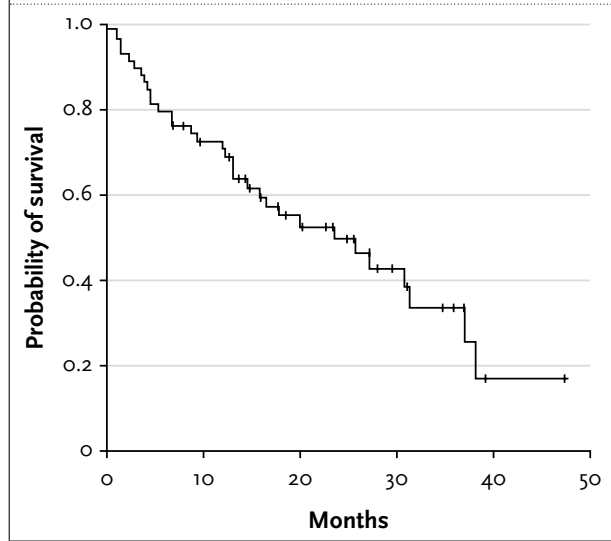
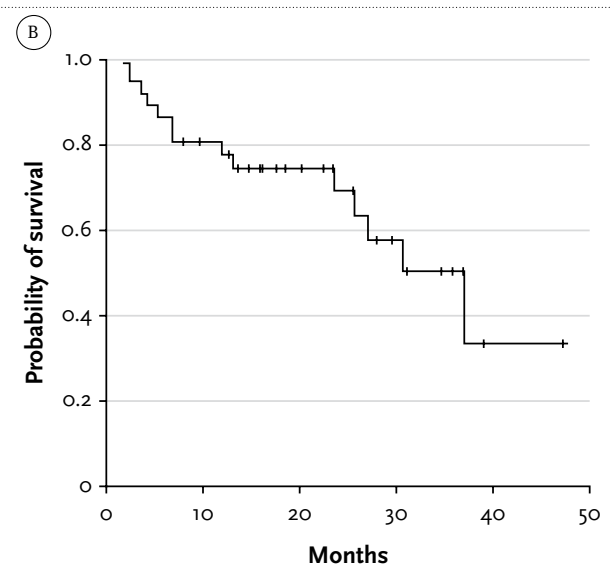
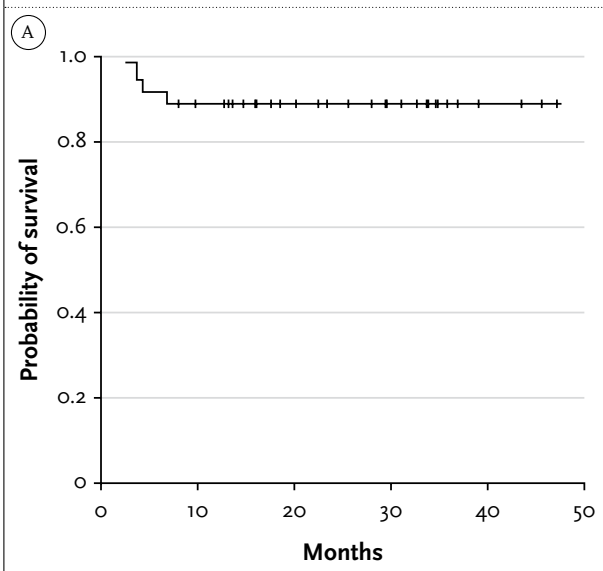


Figure 3. A: Overall survival in patients who received NMA as first-line treatment. B: Progression-free survival in patients who received NMA as first-line treatment



survival ($p=0.012$) but not with progression-free survival ($p=0.3$). The 11 patients with acute GvHD grade III and IV had inferior overall survival due to fatal outcome of this complication in five patients ($p=0.001$). No fatal deaths were observed in the patients with acute GvHD grade 0 to II. None of all other factors tested including age, gender of recipient or donor, conditioning regimen, use of ATG, family or a matched unrelated donor, deletion of chromosome 13 (FISH), β_2 microglobulin ≥ 3 mg/ml, had an impact on overall or progression-free survival. In the patients who received NMA as part of the treatment for relapsed myeloma overall survival and progression-free survival at two years were 77.5 and 23.9%, respectively

(figure 5). None of the factors tested including age, gender as described above had an impact on progression-free and overall survival. It should be mentioned, however, that the statistical analysis must be interpreted with caution due to the small number of patients.

Toxicity

Nonrelapse mortality at 12 months was 12% (figure 6). Five patients (9%) died from acute GvHD grade III to IV. One patient died from complications occurring after heart catheterisation and one relapsed patient refused further treatment, including a stem cell boost for secondary aplasia and ultimately died from overwhelming septicaemia. Acute

Figure 4. A: Overall survival in patients who received NMA as first-line treatment and did reach complete remission afterwards and patients who did not reach complete remission. B: Progression-free survival in patients who received NMA as first-line treatment and did reach complete remission afterwards

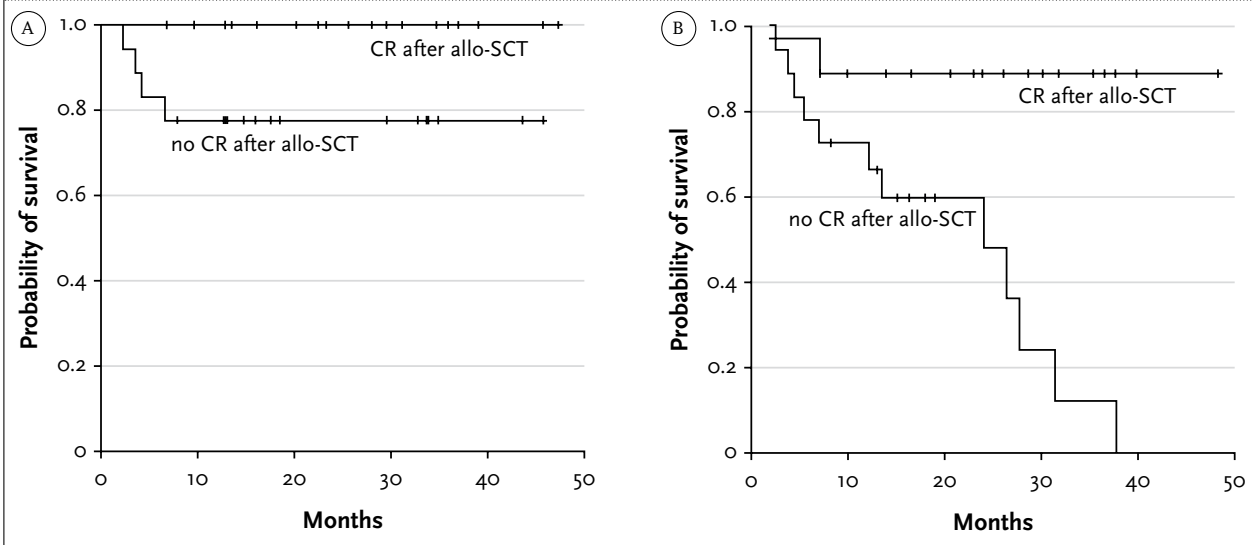
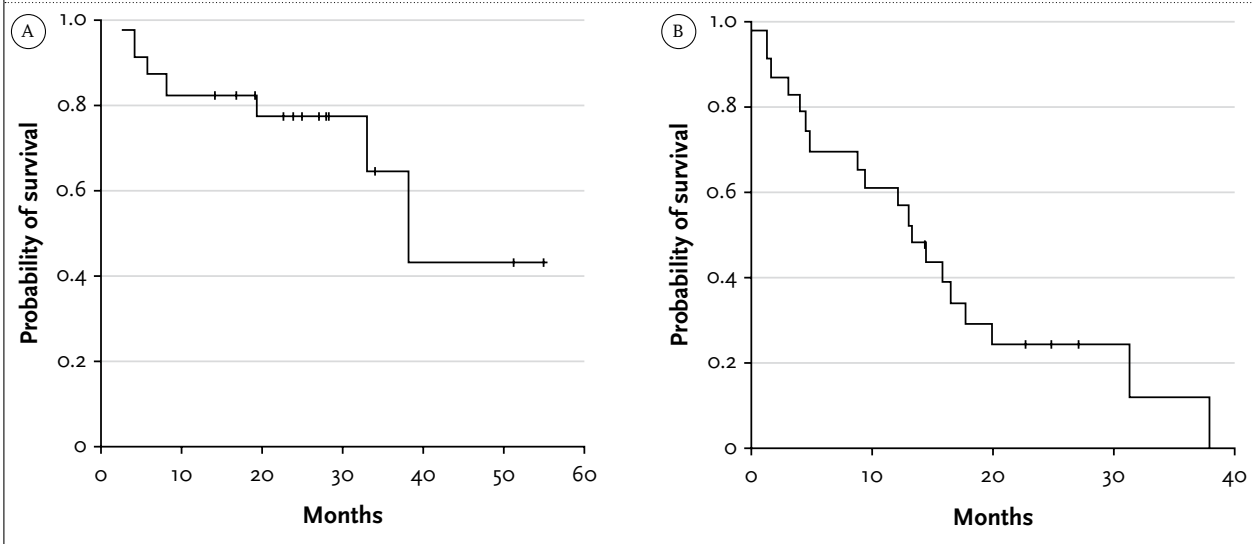


Figure 5. A: Overall survival in patients who received NMA as treatment for relapsed myeloma. B: Progression-free survival in patients who received NMA as treatment for relapsed myeloma

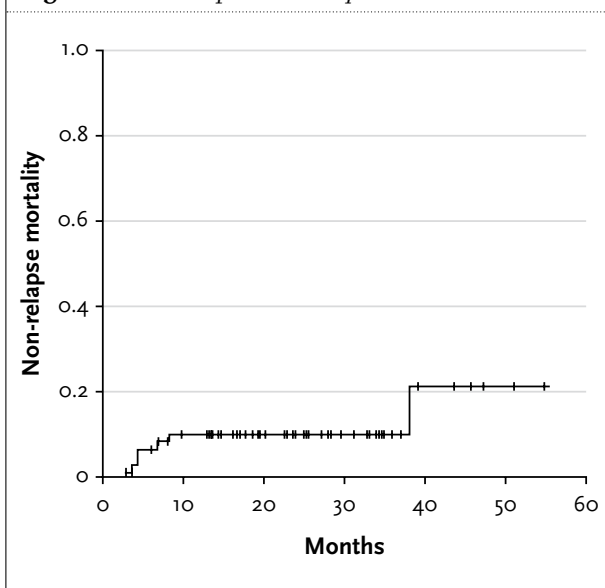


GvHD following NMA occurred in 38 patients (64%): grade I in 12 (20%), grade II in 12 (20%), and grade III or IV in 14 patients (24%). Chronic GvHD following NMA occurred in 32 patients (54%), with three patients (5%) experiencing limited disease and 29 patients (49%) extensive disease. NMA as first-line treatment was associated with a higher incidence of grades II to IV acute GvHD, when compared with NMA as relapse treatment (56 vs 26%; $p=0.034$). The use of ATG significantly reduced the incidence of chronic GvHD (20 vs 66%; $p=0.003$). This may explain the lower incidence of chronic GvHD in patients with an unrelated or mismatched donor. All other factors tested were not associated with occurrence of chronic or acute GvHD.

DISCUSSION

Several conclusions can be drawn from this retrospective study. The first one is that NMA is feasible in multiple myeloma, even in heavily pretreated patients. Nonrelapse mortality after NMA compares very favourably with nonrelapse mortality after myeloablative ASCT.^{4,5} What is remarkable is the absence of nonrelapse mortality in the patients receiving a transplant from a matched unrelated donor, probably due to the administration of ATG. The second observation is that NMA as part of first-line therapy results in a high percentage of complete responses which seems to be predictive for prolonged progression-free and

Figure 6. Nonrelapse mortality



overall survival, while all patients not achieving a complete response, including the vast majority of the relapsed patients, have remissions of short duration. Longer observation, however, is needed to determine the quality and durability of these complete remissions. Late relapses from complete remissions are not uncommon after ASCT for multiple myeloma.¹³ The third conclusion is that overall survival is remarkably good even in the pretreated patients. This may be due to the efficacy of novel agents such as thalidomide, bortezomib and DLI given to the patients who relapsed after NMA.^{14,15} Acute and chronic GvHD were the most important toxicities and responsible for the fatal outcome in five patients (9%). Nonrelapse mortality percentage may still increase due to the considerable number of patients with chronic extensive GvHD. Chronic GvHD, the most important negative factor for quality of life after NMA with full stem cell grafts, is however a significant factor for prolonged progression-free and overall survival.

Although our results and results from other studies are encouraging, the role of NMA for myeloma is not yet established.^{8,16} In the recently published prospective study by the French IFM, high-risk myeloma patients with an HLA-identical family donor and treated with tandem autologous/NMA-ASCT had comparable progression-free and overall survival to the patients with no donor who were treated with double autologous SCT.¹⁸ In this study *in vivo* T-cell depletion was performed with high-dose ATG as part of the nonmyeloablative conditioning regimen in all patients. The beneficial effect of *in vivo* T-cell depletion is the low incidence of acute and chronic GvHD; the detrimental effect is the elimination of the graft vs myeloma (GvM) effect.¹⁹ The importance of immune-competent donor T cells for graft vs myeloma effect is

illustrated by responses to DLI and the occurrence of chronic GvHD.²⁰ European study groups, including the Dutch Haemato-Oncology Association (HOVON), Spain's Programa para el estudio y tratamiento de las hemopatias malignas (PETHEMA), and the European Group for Blood and Marrow Transplantation (EBMT), are performing comparable prospective donor vs no-donor studies. The results of these studies have to be awaited for more definite conclusions about the value of NMA in multiple myeloma. In anticipation of the outcome of these studies it is necessary to explore new strategies which are aimed at stimulating the cytotoxic efficacy of the donor T cells towards the residual myeloma cells without enhancing GvHD. The suggestion that the novel antimyeloma agents such as bortezomib, thalidomide, and lenalidomide may preferentially stimulate the graft-vs-tumour effect and not GvHD is fascinating in this respect.^{21,14}

In conclusion, NMA ASCT as part of first-line treatment of multiple myeloma is feasible, is associated with acceptable transplant-related mortality and may induce a high percentage of complete remissions of good quality and prolonged duration. The outcome of prospective donor vs no donor studies, however, has to be awaited to better define the role of this treatment for multiple myeloma. In extensively pretreated patients response rate and progression-free survival are disappointing and in this category of patients new strategies need to be explored. These strategies should be aimed at enhancing the graft-vs-tumour effect probably by incorporating novel agents.

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