

Prognostic factors in allogeneic transplantation for patients with high-risk multiple myeloma after reduced intensity conditioning

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Objectives. The aim of this study was to identify prognostic factors for outcome of high-risk patients with multiple myeloma after allogeneic transplantation prepared by reduced intensity conditioning (RIC).

Materials and Methods. Data from 45 consecutive patients (median age 52 years, range 38–68), who received grafts from a sibling (n = 34) or unrelated donor (n = 11) were analyzed. Fourteen patients received an RIC allotransplant while chemosensitive (\geq partial remission [PR]), whereas 31 chemoresistant patients ($<$ PR) had either relapsed (n = 28) or were refractory (n = 3) after one or more autografts; of these 28 patients, 4 had secondary myelodysplasia concurrent with relapse. Of the 14 chemosensitive patients, 12 received an RIC allotransplant as consolidation after an autotransplant (AT).

Results. Twenty-nine (64%) were in a complete remission (CR) or near CR, 5 were in PR, and 5 had progressive disease. Twenty-five patients died, 17 of transplant-related complications, 7 of progressive disease, and 1 of a nontransplant-related cause. With a median follow-up of 15 months, the following factors were significantly associated with a better event-free survival (EFS) probability at 3 years: chemosensitive disease (64% vs 12%), pretransplant performance score (PS, Zubrod) \leq 2 (36% vs 0%), CR + near CR post transplant (36% vs 0%), and presence of chronic graft-vs-host disease (GVHD; 29% vs 0%). The same factors and absence of grade III to IV acute GVHD (52% vs 0%) were significant for a better overall survival (OS). On multivariate analysis including only pretransplant factors, both chemosensitive response and PS \leq 2 were significant for overall survival and event-free survival ($p < 0.01$). When response to RIC allotransplant and GVHD were added to the model, chronic GVHD was significant for better event-free survival, with an odds ratio of 1.5 ($p < 0.01$).

Conclusion. Our data suggest that although RIC allotransplant induces high rates of CR and near CR, even in refractory disease, it appears to result in a durable response only if it is applied early in the disease in high-risk patients, when they still are chemosensitive and have an adequate PS. © 2003 International Society for Experimental Hematology. Published by Elsevier Science Inc.

Autologous stem cell transplantation after high-dose myeloablative therapy has increased complete remission (CR) rates up to 50% in patients newly diagnosed with myeloma, resulting in a significant increase in event-free survival

(EFS) and overall survival (OS) compared to conventional therapy [1–3]. Although a substantial fraction of patients remains alive and disease-free for more than 10 years, the frequency of disease progression or relapse continues to be high after transplantation in patients with poor prognostic features at presentation, such as chromosome 13 abnormalities, hypodiploidy, or high β_2 microglobulin levels before first autotransplant (AT) [4,5].

Although myeloablative allogeneic stem cell transplanta-

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tion uses a stem cell source that is not contaminated with myeloma cells and induces a graft-vs-myeloma effect [6], the survival rates have been inferior to those after ATs because of high transplant-related mortality (TRM) [7–9]. We and other groups have reported promising results in multiple myeloma with allotransplants after nonmyeloablative conditioning, resulting in a decrease in TRM [10–12]. However, after 3 years of experience with this procedure, we have observed a significant divergence in survival of patients according to their disease status at the time of reduced intensity conditioning (RIC). Our results show that although RIC allotransplant induces high CR and near CR rates, it does not produce durable disease control in refractory or relapsing patients after ATs. Only patients with high-risk myeloma after a single AT appear to obtain long-term disease control with an RIC allotransplant, whereas tandem ATs are noncurative in such patients.

Patients and methods

Patient and disease characteristics

Between June 1998 and March 2002, 45 multiple myeloma patients between ages 35 and 70 years were prospectively entered into a study providing RIC allotransplant using a related ($n = 34$) or unrelated donor ($n = 11$) at the Myeloma Institute for Research and Therapy of the University of Arkansas for Medical Sciences. The treatment protocol was approved by the Institutional Review Board of the University of Arkansas for Medical Sciences, and an informed consent was obtained from all patients and donors. Preliminary outcome data have been reported previously [10,11]. The demographic data are given in Table 1. Patient flow and responses to different therapeutic interventions are shown in Figure 1. At the time of RIC, 40 patients (89%) showed high-risk disease based on the presence of unfavorable karyotypes [5]. All patients had received at least one autograft, with 22 patients having one, 19 having two, and 4 having three prior ATs. Overall, 14 patients (31%) showed chemosensitive disease (5 CR, 3 near CR, 6 partial remission [PR]) before RIC, including the 12 patients who received an RIC allotransplant as consolidation therapy after one prior AT, and 31 patients (69%) were chemoresistant to salvage therapy for re-

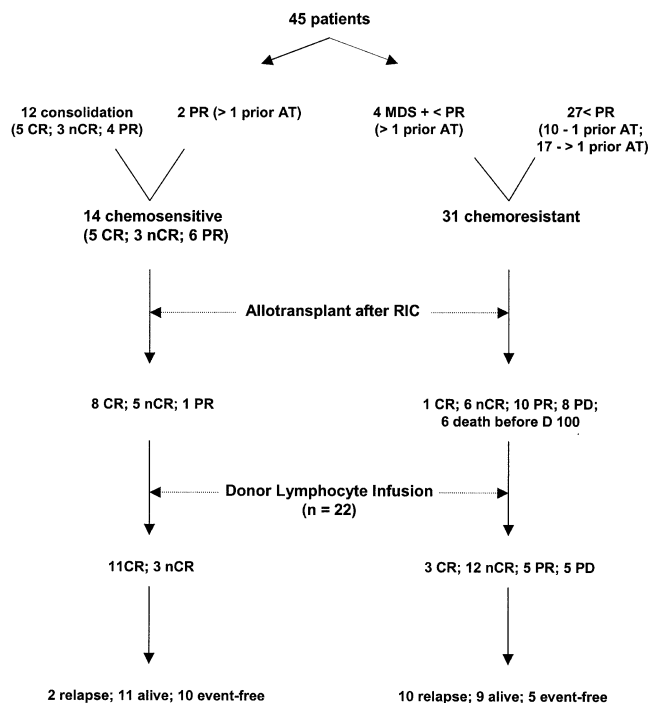


Figure 1. diagram of the 45 patients. AT = autotransplant; CR = complete remission; nCR = near complete remission; PD = progressive disease; PR = partial remission; RIC = reduced intensity conditioning.

lapsed myeloma after AT. Median age of the 14 patients was 52 years (range 38–65), compared with median age of 53 years of the remaining 31 patients (range 38–68). Of the 12 patients who received an RIC allotransplant as consolidation, 10 had chromosome 13 abnormality, and 2 had complex chromosomal abnormalities without chromosome 13 abnormality but attained only PR after a single AT. The remaining 33 patients (73%) had either relapsed after ($n = 26$) or were refractory ($n = 3$) to prior AT, or had developed treatment-related myelodysplastic syndrome concurrent with relapsing myeloma ($n = 4$). Median interval between the last pre-allotransplant therapy and the RIC allotransplant was 106 days (range 4–812); 84 days (range 20–812) for patients with relapsed/refractory disease and 107 days (range 84–264) for patients who received an RIC allotransplant as consolidation.

Table 1. Patient and disease characteristics at the time of reduced intensity conditioning

Parameter	Median	Range	Cutoff	No. of patients
Age (yr)	52	38–68	(>50)	27 (60%)
β_2 microglobulin	3	1.3–73.7	(>4.0)	17 (38%)
C-reactive protein (mg/L)	2.8	0.1–79	(>4.0)	12 (27%)
Creatinine clearance (mL/min)	99	4–197	(<75)	15 (33%)
Albumin (gm/dL)	3.9	2.1–5.2	(<3.5)	13 (29%)
Lactate dehydrogenase (IU/L)	165	111–722	(>200)	12 (27%)
Zubrod performance score	2	0–3	(>2)	17 (38%)
Cytogenetics				
–13, del13q				33 (73%)
Other abnormalities				7 (16%)
Male:Female				31:14
IgA myeloma				12 (27%)

Study design

A standard two-stage microcytotoxicity assay was used to test class I HLA antigens. Class II HLA antigens were assessed by allele typing of DRB1 with sequence specific oligonucleotide hybridization. When identical at HLA-A, HLA-B, and D/DRB1 loci, donor and patient pairs were considered matched. Donors also were acceptable if HLA class I antigens mismatched by a single split or single disparity in the same cross-reactive group ($n = 3$), or HLA class II by a single high-resolution DNA-DRB1 disparity ($n = 2$).

The conditioning regimen for RIC consisted of intravenous melphalan 100 mg/m² over 20 minutes on day –1 for sibling allotransplants, and the same dose of melphalan plus total body irradiation 125 cGy bid on day –2 and fludarabine 30 mg/m² on days –2 and –1 for unrelated transplants. The intensity of the conditioning

regimen for unrelated transplants was increased to compensate for minor HLA antigen disparity. Intravenous cyclosporine 3 mg/kg/day was started on day -1 and subsequently changed to oral dose when tolerated to maintain whole blood trough levels at 300 ng/mL. Patients receiving unrelated allotransplant were given additional methylprednisolone 1 mg/kg/day, starting on day 5, with subsequent tapering and discontinuation by day 29 if there was no evidence of graft-vs-host disease (GVHD). Combination of cyclosporine with corticosteroid were given as initial therapy for acute GVHD grade \geq II and chronic GVHD.

All sibling ($n = 34$) and eight unrelated donors were mobilized with granulocyte colony-stimulating factor (G-CSF), and stem cells were collected using large-volume leukaphereses to achieve greater than 5×10^6 CD34⁺ cells/kg of recipient body weight. Three unrelated donors preferred a bone marrow harvest. Two mismatched unrelated grafts were T cell depleted using CD34⁺ cell selection (Isolex, Nexell Therapeutics, Inc., Irvine, CA, USA). Median number of CD34⁺ cells and CD3⁺ cells in the graft was 5.1×10^6 /kg (range 1.5–12.5) and 1.7×10^8 /kg (range 0.1–5.1), respectively. The two T-cell-depleted grafts contained 1×10^5 and 3×10^5 CD3⁺ cells/kg, respectively.

Initially, cyclosporine taper started on day 60 in the absence of acute GVHD. After the accrual of 22 patients, however, taper of cyclosporine was delayed until day 120 because of a high incidence of acute GVHD with early tapering. For the first 16 patients, increasing doses of donor CD3⁺ cells (1×10^5 to 1×10^7 CD3⁺ cells/kg) were given on days 21, 42, and 112 to patients with mixed chimerism and no acute GVHD. Because of a high rate of acute GVHD after donor lymphocyte infusion (DLI), decisions on DLI for the remaining 29 patients were made on the basis of incomplete donor chimerism and inadequate disease response after RIC allotransplant. Six additional patients received DLI, resulting in a total of 22 patients with DLI. Patients with mixed chimerism and no acute GVHD ($n = 4$) received DLI while taking cyclosporine, and patients with residual or recurrent disease ($n = 2$) received DLI in the absence of acute GVHD after they had discontinued all immunosuppression. Salvage chemotherapy was administered to 10 patients who relapsed or showed persistent bulky disease after RIC, before additional DLI without prophylactic cyclosporine.

Antibacterial, antifungal, and antiviral prophylaxis was administered according to institutional protocols, including sulfamethoxazole-trimethoprim and acyclovir up to 6 months after transplant. Itraconazole 400 mg/day was started before the transplant and continued until CD4⁺ count exceeded 400/ μ L. Patients at high risk of fungal infection and those unable to tolerate oral itraconazole received intravenous liposomal amphotericin-B 1 mg/kg/day. Cytomegalovirus antigenemia was assessed weekly, and ganciclovir/foscarnet was given to patients with a positive test result (≥ 2 positive cells/slide) as a preemptive therapy.

Statistical analysis

Patients were prospectively evaluated for engraftment, chimerism, TRM, incidence of acute and chronic GVHD, response to transplant, relapse, and death. The day of myeloid engraftment was defined as the first of 3 consecutive days of an absolute neutrophil count (ANC) of 0.5×10^9 /L or more. Platelet recovery was considered to have occurred when the platelet counts increased spontaneously to 50×10^9 /L or more for 7 days. Donor-recipient chimerism was assessed monthly on blood and marrow by polymerase chain reaction test for the loci of variable number of

tandem repeat in sex-matched transplants and fluorescent in situ hybridization (FISH) test for the Y chromosome in sex-mismatched transplants according to published methods [13]. Mixed chimerism was defined as the presence of more than 5% donor or host-derived cells. Acute and chronic GVHD were graded according to published criteria [14,15].

CR required the disappearance of monoclonal gammopathy in serum and urine on immunofixation analysis and attainment of normal bone marrow aspirate and biopsy with < 1% light chain-restricted plasma cells on flow cytometry, on at least two successive occasions at least 2 months apart [16]. Cases were considered to be near CR if bone marrow findings were normal and positive immunofixation analysis of serum or urine was the only evidence of disease. PR implied a normal marrow aspirate and biopsy and at least 75% reduction from baseline serum M protein and/or, in case of Bence Jones proteinuria, reduction to less than 100 mg/day.

Chemosensitive response before the RIC was defined as attainment of CR + near CR + PR by the preceding chemotherapy. TRM was defined as any death due to complications related to the RIC allotransplant. Events were defined as either death or relapse/disease progression. Relapse was defined as recurrence of monoclonal protein or bone marrow plasmacytosis or evidence of extramedullary disease in case of CR or near CR or any new disease manifestation, including hypercalcemia. Disease progression for non-CR patients implied at least a 25% increase in tumor mass or any new disease manifestation.

Pretransplant variables analyzed were response to the last treatment before RIC allotransplant (chemosensitivity), RIC performed as consolidation after a single AT vs for relapse or refractory disease, cytogenetic findings (chromosome 13 abnormalities present vs absent), and Zubrod performance score (PS ≤ 2 vs > 2). Variables related to RIC allotransplant included type of donor (related vs unrelated), response to RIC allotransplant, and development of acute/chronic GVHD. Categorical variables were analyzed by the frequency table with Fisher's exact or Pearson's Chi-square test. Patients who had evidence of myeloid engraftment were evaluable for acute GVHD, and the day 100 posttransplant was applied as a landmark point for analysis of chronic GVHD and response posttransplant. Cumulative incidence curves were generated to calculate the probability of chimerism, acute and chronic GVHD, TRM, responses, and relapse, using the NCSS statistical software, version 2001 [17,18]. A competing risk for chimerism was death before the first assessment of chimerism; for TRM, relapse; for chronic GVHD, death without chronic GVHD; for acute GVHD, death without acute GVHD; and for response, death without response, respectively. Survival curves were estimated using the product limit method of Kaplan-Meier method, and the log rank test was used for comparison [19,20]. Cox proportional hazards regression [19] was used to assess the influence of prognostic factors on survival outcomes. For multivariate analyses, variables with $p < 0.1$ in univariate analysis were entered into a stepwise multivariate regression by the Cox proportional hazard model [19].

Results

Engraftment

Myeloid engraftment (ANC $> 0.5 \times 10^9$ /L) occurred at a median of 12 days (range 8–46), and median time to platelet

recovery ($\geq 50 \times 10^9/L$) was 23 days (range 15–62). Thirty-six patients (80%) achieved full donor chimerism by day 56, and 42 patients (93%) (5 after DLI) by day 156 (Fig. 2A). Of these, 32 (94%) with a sibling allotransplant and 10 patients (91%) with an unrelated allotransplant reached full donor chimerism ($p = 0.67$). Two patients with a sibling allotransplant lost initial full donor chimerism on days 53 and 62, followed by disease relapse on days 140 and 119, respectively. One of the unrelated recipients who received an HLA-mismatched, T-cell-depleted graft maintained transient mixed chimerism lasting for less than 4 weeks before graft rejection. All three patients recovered spontaneously to autologous reconstitution of marrow function.

Graft-vs-host disease

Thirty-five patients (78%) developed acute GVHD. Nineteen patients (42%) had grade III to IV acute GVHD, resulting in five deaths; 16 (36%) had grade I to II acute GVHD with no deaths (Fig. 2 B). All three HLA-mismatched sibling recipients developed grade III to IV acute GVHD, resulting in two deaths. Six of 11 unrelated recipients had acute GVHD (3 grades I–II; 3 grades III–IV), compared with 29 of 34 related patients (13 grades I–II; 16 grades III–IV) ($p < 0.05$). Two unrelated recipients who received a T-cell-depleted HLA-mismatched allotransplant did not develop acute GVHD.

Twenty-six patients (58%) developed chronic GVHD (10 limited and 16 extensive) (Fig. 2C). Five of seven patients without acute GVHD developed de novo chronic GVHD, including three after DLI. Three of four evaluable unrelated and 23 of 27 related patients developed chronic GVHD ($p = 0.52$). Only one of these patients (sibling recipient) died of chronic pulmonary GVHD 20 months after transplant.

Donor lymphocyte infusion

Twenty-two of the 45 patients received post-RIC DLIs: 12 received one, 5 received two, and 5 patients had three DLIs. All except two patients who received DLI were sibling recipients. Fourteen patients received DLI for inadequate disease control: 10 after further posttransplant chemotherapy and 4 without additional chemotherapy. The other eight patients had already achieved CR or near CR after RIC allotransplant and received DLI only because of mixed chimerism. Of these eight patients, five achieved full donor chimerism. Three of these five patients relapsed on days 162, 168, and 221, respectively. Two patients with sibling allotransplant who became mixed chimeras after initial full donor chimerism and one unrelated recipient with mixed chimera from a T-cell-depleted graft did not respond to subsequent DLI. The other patient with an unrelated allotransplant received DLI for disease control.

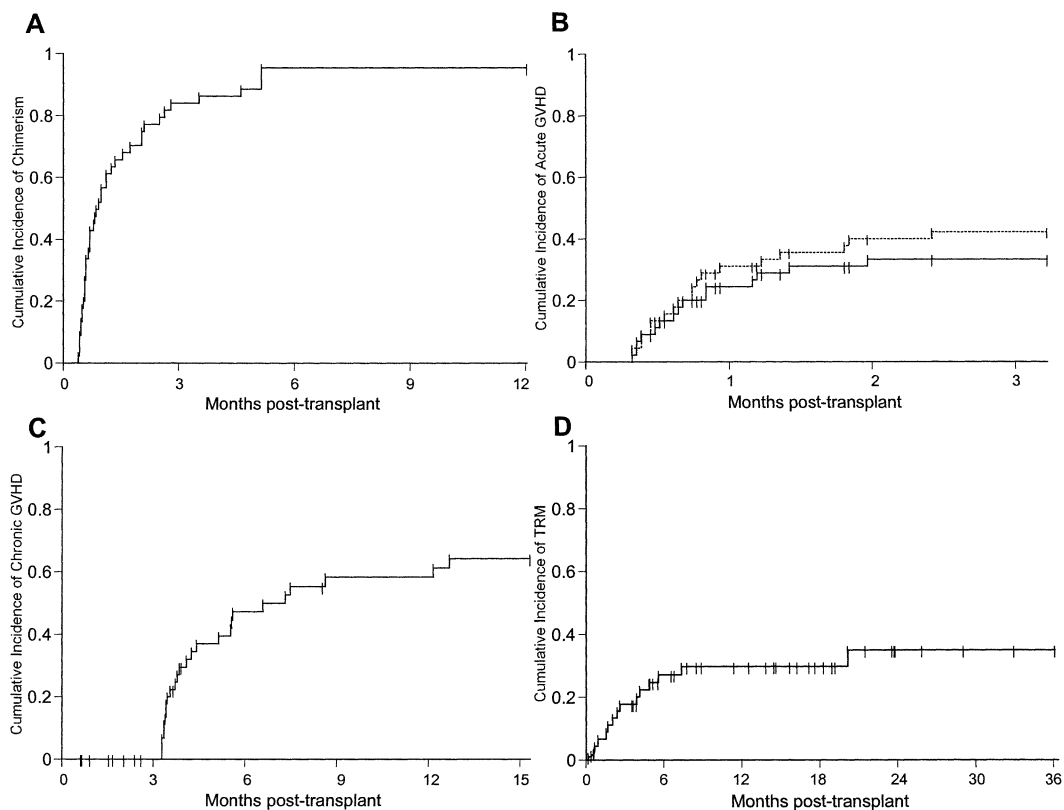


Figure 2. Cumulative incidence curves. (A) Chimerism. (B) Acute graft-vs-host disease (GVHD). Solid line = grades I–II; dotted line = grades III–IV. (C) Chronic GVHD. (D) Transplant-related mortality.

Seventeen of the 22 patients who received DLI developed acute GVHD: 13 after one and 4 after two DLI. None of the five patients who received three DLI showed acute GVHD. Of the two unrelated recipients, only one developed grade III acute GVHD. Eight of the 10 patients (all sibling recipients) who received posttransplant chemotherapy and DLI developed both acute (1 grade II; 6 grade III; 1 grade IV) and chronic GVHD. None of these patients died of acute GVHD, but one died of chronic GVHD of the lungs.

Transplant-related mortality

Seventeen patients (38%) died of transplant-related causes (Fig. 2D): GVHD ($n = 6$), invasive fungal infection ($n = 5$), other infections ($n = 4$), idiopathic pneumonia ($n = 1$), or heart failure ($n = 1$). Six patients died before day 100 (13%), and 14 during the first 6 months post-RIC (31%); the other three died at days 224, 271, and 615, respectively. All patients with invasive fungal infections had been treated with high-dose corticosteroids to control acute GVHD. The one patient who developed idiopathic pneumonia had received two ATs with melphalan 200 mg/m² before RIC. One patient who died of heart failure had received a cumulative dose of doxorubicin 560 mg/m² before RIC. Of the 12 patients who received RIC for consolidation, one died of acute GVHD and the other of suicide.

Disease response, survival, and relapse. Of all patients, 29 patients achieved CR ($n = 14$) or near CR ($n = 15$), including eight patients in CR ($n = 5$) or near CR ($n = 3$) before RIC allotransplant. Of 37 patients in less than near CR before RIC allotransplant, 21 achieved CR ($n = 9$) or near CR ($n = 12$), with a 1-year cumulative incidence of 61% (Fig. 3A). Five additional patients achieved PR and the remaining five showed no response. All responses occurred within 1 year after transplant, with a median time to maximal response of 111 days (range 14–375). Nine patients achieved their maximal response only after DLI. Of the 10 patients who received posttransplant chemotherapy and DLI, six attained CR ($n = 4$) or near CR ($n = 2$). Three of the four patients who received DLI for disease control without chemotherapy also showed an excellent response (1 CR and 2 near CR).

Median overall survival of all patients from RIC allotransplant was 14 months, and estimated 3-year OS probability is 36%. Median follow-up time for surviving patients was 18 months. Median EFS was 7 months for all patients, with estimated 3-year EFS probability of 13%. Twelve patients relapsed, with a 3-year cumulative incidence of 42%. Five of the 29 patients who achieved CR ($n = 1$) or near CR ($n = 4$) after RIC allotransplant relapsed, but no relapses have yet been observed in patients receiving RIC allotransplant as consolidation. Two of the 14 chemosensitive patients and 10 of the 25 evaluable chemoresistant patients relapsed (0/3 in CR, 4/12 in near CR, 6/10 in less than near CR after RIC).

In a subset analysis of the 22 patients who received a single AT before RIC, the 12 patients transplanted as consolida-

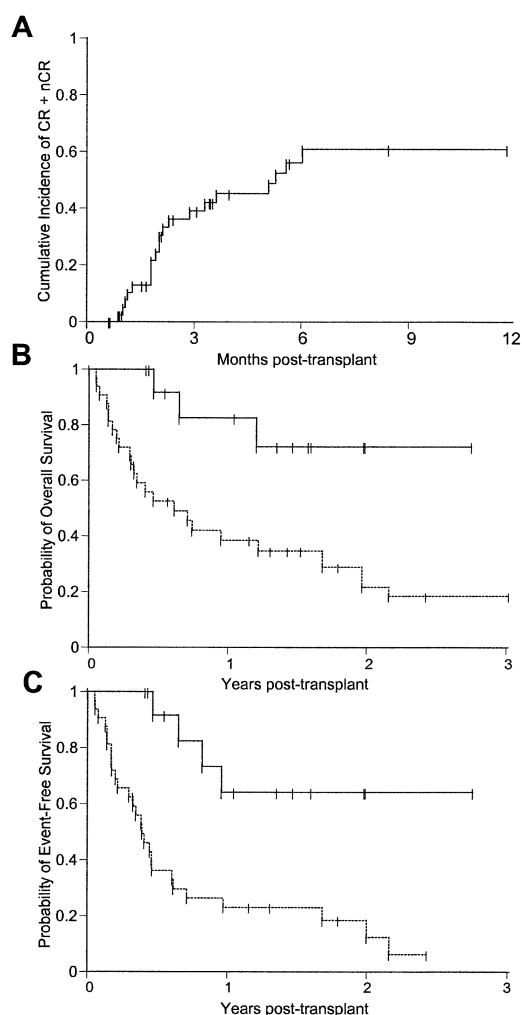


Figure 3. (A) Cumulative incidence of complete remission (CR) + near complete remission (nCR) of the 21 patients with remaining disease at the time of reduced intensity conditioning allotransplant. (B) Probability of overall survival in chemosensitive (solid line) and chemoresistant patients (dotted line). (C) Probability of event-free survival in chemosensitive (solid line) and chemoresistant patients (dotted line).

tion had a 3-year OS probability of 80% compared with 19% in the 10 patients with relapsed or refractory myeloma ($p = 0.01$). The 3-year EFS probability for the 12 consolidation patients was 80% vs 0% in the 10 other patients ($p = 0.004$).

Unrelated donor transplantation. The median age of the unrelated recipients was 48 years (range 38–64) compared with 53 years (range 38–68) of the related recipients ($p = 0.19$). Two patients received unrelated grafts for consolidation and 10 after relapse. Both median OS and EFS were 3 months, and the estimated 1-year OS probability was 27% because of a significant TRM rate of 45%. All cases of TRM were infection related. Of the remaining six patients, only one had relapse.

Univariate and multivariate analyses. Table 2 lists the factors that affect overall survival. Median survival from RIC

Table 2. Univariate factors affecting overall and event-free survival (Kaplan-Meier)

Factors	3-yr OS* (<i>p</i>)	3-yr EFS* (<i>p</i>)
Chemosensitive disease before RIC		
≥PR vs <PR	72% vs 18% (0.03)	64% vs 6% (0.002)
Chromosome 13 abnormality		
Absent vs present	35% vs 15% (NS)	27% vs 18% (NS)
Zubrod performance score		
≤2 vs >2	47% vs 10% (0.0004)	34% vs 7% (0.01)
Response to RIC allotransplant [†]		
CR/nCR vs <nCR	46% vs 19% (0.06)	33% vs 0% (0.004)
Grades of acute GVHD		
0–2 vs 3–4	46% vs 0% (0.07)	17% vs 15% (NS)
Chronic GVHD [†]		
Present vs absent	42% vs 30% (NS)	30% vs 0% (0.01)

*Kaplan-Meier estimate of 3-year survival probability.

[†]Response and chronic graft-vs-host disease (GVHD) based on day 100 landmark.

CR = complete remission; EFS = event-free survival; nCR = near complete remission; NS = not significant ($p > 0.1$); OS = overall survival; PR = partial remission; RIC = reduced intensity conditioning.

allotransplant for chemosensitive patients ($n = 14$) has not been reached, but it was 7.5 months for chemoresistant patients ($n = 31$) (3-year OS probability 72% vs 18%, $p = 0.004$) (Fig. 3B). Median survival of patients ($n = 12$) who received RIC allotransplant as consolidation has not been reached, but it was 8.5 months for all of the other patients (3-year OS probability 80% vs 9%, $p = 0.01$). Patients ($n = 28$) with Zubrod PS ≤2 had a median survival of 25.5 months vs 4 months for patients ($n = 17$) with PS >2 (3-year OS probability 47% vs 10%, $p = 0.0004$). Using a 100-day landmark analysis ($n = 39$), median survival for patients who achieved CR or near CR after RIC allotransplant ($n = 29$) was 23 months compared with 8 months for the other patients ($n = 12$) (3-year OS probability 46% vs 19%, $p = 0.06$). Patients with grade 0 to II acute GVHD ($n = 23$) had a median survival of 20 months compared with 4.5 months for patients with grade III to IV acute GVHD ($n = 19$; 3-year OS probability 46% vs 0%, $p = 0.07$).

Median EFS for chemosensitive patients has not been reached, but it was only 4.5 months for chemoresistant patients (3-year EFS probability 64% vs 6%, $p = 0.002$) (Fig. 3C). Median EFS for patients who received RIC allotransplant as consolidation has not been reached, but it was 5 months for the other patients (3-year survival probability 80% vs 0%, $p = 0.0001$). Patients with Zubrod PS ≤2 had a median EFS of 23 months vs 4 months for patients with PS > 2 (3-year EFS probability 34% vs 7%, $p = 0.01$). Median EFS for patients who achieved CR or near CR after RIC allotransplant was 12 months compared with 4.5 months for patients with less than near CR (3-year EFS probability 33% vs 0%, $p = 0.004$). Patients with chronic GVHD ($n =$

Table 3. Multivariate analysis of prognostic variables with hazard ratio (HR) and *p* value

	OS		EFS	
	HR	<i>p</i>	HR	<i>p</i>
Pretransplant factors				
Chemosensitive disease	1.6	0.009	1.4	0.004
PS ≤2	1.3	0.002	1.1	0.004
Pre- and posttransplant factors				
Chemosensitive disease	1.6	0.01	1.6	0.005
PS ≤2	1.3	0.002	1.0	0.009
CR/nCR after RIC allotransplant	0.1	NS	.5	NS
Acute GVHD grades 0–II	0.6	NS	NA	NA
Present chronic GVHD	NA	NA	1.5	0.005

NA = not applicable; NS = not significant ($p > 0.05$). Other abbreviations as in Table 2.

26) had a median EFS of 23.5 months compared with 5.5 months for patients with no chronic GVHD ($n = 6$) (3-year EFS probability 30% vs 0%, $p = 0.01$).

On multivariate analysis including only pretransplant factors, both chemosensitive disease and PS ≤2 were good prognostic factors for both OS and EFS (Table 3). When response to RIC allotransplant and GVHD (acute GVHD for OS; chronic GVHD for EFS) were added to the analysis with the pretransplant factors and a 100-day landmark was applied, chemosensitive disease and PS ≤2 remained favorable for both OS and EFS, and presence of chronic GVHD was favorable for EFS.

Discussion

The current study confirms our initial observation in a larger group of patients with a longer follow-up that there are significant differences in outcome between two groups of patients, i.e., patients with relapsed or refractory disease after AT vs chemosensitive patients with excellent disease control before RIC. Our study suggests only a very limited role of RIC allotransplant for patients relapsing after ATs. Patients with chromosome 13 abnormalities who fare poorly even with tandem AT appear to do much better with a single AT followed by RIC allotransplant; the absence of relapse so far in the 12 high-risk disease patients who received RIC allotransplant as consolidation suggests that the graft-vs-myeloma effect is exploited optimally when the myeloma burden is minimal and when tumor cells still are sensitive to chemotherapy. This is confirmed by the preliminary data with a single AT followed by allotransplantation after nonmyeloablative preparation reported by the Seattle group [21]. The group of patients who relapsed after AT fared very poorly, despite a high CR/near CR rate, and a high incidence of acute/chronic GVHD after allotransplantation. All relapses occurred less than 2 years after transplant. PS exerted a significant influence on survival; 14 of the 17 patients with PS >2 died, with 6 deaths of TRM within day 100. Although RIC has allowed patients with co-

morbid conditions to receive allogeneic transplantation, the high incidence of TRM in patients with a poor performance status suggests that although a low-intensity conditioning regimen is well tolerated, patients with a poor performance status are unable to survive the consequences of GVHD and its treatment.

In contrast to patients with severe acute GVHD (grades III–IV) who had an inferior outcome, patients with chronic GVHD had a superior survival. Our experience with conventional allotransplants and RIC allotransplants in multiple myeloma indicates that long-term disease control is seen only in patients who developed chronic GVHD, indicating that the graft-vs-myeloma effect is mostly directed against disparities in either major or minor histocompatibility antigens and not against a myeloma-associated tumor antigen. The high relapse rate in our study, despite the significant incidence of both acute and chronic GVHD, suggests the contribution of GVHD to disease control is relatively weak compared with graft-vs-leukemic activity in patients with other hematologic malignancies such as chronic myelogenous leukemia.

In a study investigating a role of further salvage transplantation for patients relapsing after ATs, the response rate was high but short lived in the majority of patients, resulting in a 2-year overall survival rate of 19% [22]. In patients with conventional allogeneic transplantation, TRM was high, similar to the experience with second allogeneic transplantation in patients with leukemia relapse after a first allotransplant [23], but resulted in a better 2-year progression-free survival than AT. Although the patients were heavily pretreated and the majority had high-risk disease, conventional allogeneic transplantation remains a challenging treatment in patients relapsing after ATs. The potential benefit of graft-vs-myeloma effect in allotransplant may be maximized if TRM decreases, which may be accomplished by nonmyeloablative conditioning or RIC. The high rate of TRM in the current study, however, suggests further prospective studies with more careful selection of patients based on performance and chemosensitivity.

In summary, our study shows both the limited role of RIC allotransplant in relapsed/refractory myeloma patients after ATs but its great potential as consolidation therapy in patients with high-risk disease who have a poor survival rate even with tandem AT. Further studies are necessary for patients with relapsed myeloma after ATs who continue to show good chemosensitive response to salvage therapy. With the regimen applied in this study, morbidity and mortality associated with acute/chronic GVHD and its treatment remain a substantial problem, preventing in our opinion the routine application of RIC allotransplant to all patients with multiple myeloma, irrespective of disease-related risk factors.

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