ORIGINAL

International Journal of Myeloma 5(3): 23–29, 2015

Outcome of allogeneic hematopoietic stem-cell transplantation for multiple myeloma: retrospective analysis of 16 patients

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The role of allogeneic hematopoietic stem cell transplantation (allo-SCT) for multiple myeloma (MM) has not yet been established. We performed allo-SCT on 16 patients with MM in our hospital and an associated center, and retrospectively evaluated its efficacy. The median age at allo-SCT was 47 years. Eight patients underwent allo-SCT as a front-line therapy. Non-myeloablative treatment was provided for 14 patients. The overall survival (OS) and progression-free survival (PFS) rates 3 years after transplantation were 72.9% and 37.5%, respectively, in patients who received front-line therapy, and were significantly higher than those in patients who received allo-SCT as salvage therapy (both $P < 0.05$). Transplant-related mortality at 3 years was 31.3%. Seven out of the 16 patients survived, and 4 patients who underwent allo-SCT as front-line therapy without maintenance showed relapse as an extramedullary mass, which was controlled by external radiation, and survived long-term, having a mean OS of 7.8 years. In our study, the OS and PFS recieved allo-SCT were not superior to those recieved more common therapies, such as autologous stem cell transplantation or combined chemotherapy with new agents. We need to have more progress in allo-SCT for MM while establishing safe and effective procedures.

Key words: multiple myeloma, allogeneic hematopoietic stem cell transplantation, graft-versus-myeloma effect

1. Introduction

New drugs (bortezomib, thalidomide, and lenalidomide) have become available in recent years, and the guidelines for treating multiple myeloma are radically changing [1]. Furthermore, achieving deeper remission before autologous peripheral blood stem cell transplantation (auto-SCT) has led to improvements in overall survival (OS), and more favorable outcomes due to the various combinations of new drugs being reported in the literature [2,3]. In spite of these drug combinations, multiple myeloma still has no cure due to the development of chemotherapy resistance during the course of prolonged treatments.

Allogeneic hematopoietic stem cell transplantation (allo-SCT) with myeloablative conditioning is no longer recommended in daily clinical medicine due to high treatment-related mortality (TRM) [4–6]. However, some clinical studies reported a 7-year progression-free survival (PFS) rate of approximately 20% among patients with multiple myeloma who underwent allo-SCT using myeloablative conditioning, and a plateau was reached in the survival curve [4–6]. These findings suggest that allo-SCT may prolong OS and be curative therapy for some multiple myeloma patients.

A non-myeloablative conditioning regimen, the so-called reduced-intensity stem cell transplantation (RIST), has recently been applied to MM patients. In 2011, two groups performed prospective studies in which therapies with auto-SCT alone versus auto-SCT followed by RIST were compared in patients with *de novo* myeloma, and favorable outcomes were observed in patients undergoing RIST [7,8]. However, allo-SCT for the treatment of multiple myeloma has not yet been estab-

Received: March 16, 2015, accepted: July 5, 2015
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lished because of a high relapse rate (RR) and TRM, even with RIST.

We retrospectively investigated the efficacy of allo-SCT in patients with MM treated in our hospital and an associated center for 11 years. We herein describe the outcomes of 16 patients with MM who underwent allo-SCT, and discuss the role of allo-SCT in the new drugs era.

2. Materials and Methods

2.1. Patients

We retrospectively reviewed 16 patients with multiple myeloma treated with allo-SCT at two institutes (Wakayama Medical University and Rinku General Medical Center) between June 2001 and December 2012. Patients with multiple myeloma were diagnosed using IMWG criteria [9]. We selected MM patients who expected to survive long time and to avoid TRM as following criteria. The inclusion criteria were: high-risk or refractory myeloma, under 60 years old and HCT-CI (Hematopoietic Cell Transplantation-Comorbidity Index) score ≤ 2. We fully explained the risks and benefits of allo-SCT to patients. After their informed consent, we provided allo-SCT for MM patients.

2.2. Definitions

We evaluated their responses and progression according to the international uniform response criteria [10]. Briefly, a partial response (PR) was defined as ≥50% reduction in serum M-protein or ≥200 mg reduction in the 24-hour excretion of Bence Jones protein (BJP) urea. A very good partial response (VGPR) was defined as ≥90% reduction in serum M-protein or ≥100 mg reduction in the 24-hour excretion of BJP urea. A complete response (CR) was defined as the complete disappearance of serum and urine M-protein using immune fixation. In addition, remission was defined as the absence of myeloma cells by morphology in marrow specimens. Cytogenetic studies were performed on bone marrow.

2.3. Statistical analysis

OS was calculated from the day of allo-SCT until death or the last follow-up. PFS was calculated from the day of allo-SCT until relapse or progression, death from any cause, or the last follow-up. The probabilities of OS and PFS were estimated using the Kaplan-Meier method. TRM and RR were estimated using the cumulative incidence method. These analyses were performed with the log-rank test to compare OS, PFS, TRM, and RR between groups. All *P*-values were 2 sided and $P < 0.05$ was considered significant. A univariate Cox regression analysis was used to determine the prognostic value of various variables for OS. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [11].

3. Results

3.1. Patient characteristics

Patient characteristics are summarized in Table 1. Median age at allo-SCT was 47 (range 31–64) years. Sixteen patients were classified by diagnosis (IgG, n = 5; IgA, n = 2; Bence-Jones protein, n = 8; non-secretory, n = 1). In addition, 12 patients had light chain κ, while 2 had light chain λ. All patients had received induction chemotherapy with vincristine, doxorubicin, and dexamethasone or new drugs (bortezomib or thalidomide). Fourteen patients had received one or two treatment regimens before allo-SCT. Only two had received more than three regimens. Eight patients had undergone high-dose therapy with auto-SCT. Eight patients with refractory/relapsed multiple myeloma had received allo-SCT as salvage therapy, while we performed it as a front-line strategy in 8 newly diagnosed patients. Three patients were found to have the deletion of chromosome 13 (del(13)) by G-banding. Seven patients had progressive disease (PD) at allo-SCT.

Table 1. Clinical characteristics of patients at diagnosis (n = 16)

Characteristics	Value
Male/female	11/5
Median age (range, years)	47 (31–64)
Myeloma subtype	
IgG	5 (31%)
IgA	2 (13%)
Bence-Jones protein	8 (50%)
Non-secretory	1 (6%)
κ/λ	12/2 (75/13%)
Deletion 13 abnormality	3 (19%)
Median time between diagnosis and allo-SCT (month)	22
Number of therapies before allo-SCT	
1–2	14 (85%)
3	1 (6%)
4–5	1 (6%)
Prior auto-SCT	
Yes/No	8/8 (50/50%)
Strategy	
Front-line/Salvage	8*/8 (50/50%)
Disease status at allo-SCT	
Non-PD	9 (56%)
PD	7 (44%)

allo-SCT, allogenic stem cell transplantation; auto-SCT, autologous stem cell transplantation; PD, progression disease.
(*) 6 patients received tandem auto/mini-allo-SCT, 2 patients received myeloablative allo-SCT.

3.2. Transplantation

Transplantation characteristics are listed in Table 2. Human leukocyte antigen (HLA) compatibility was determined by medium resolution molecular methods for HLA-A, -B, C, and -DRB1. Eight patients were transplanted from HLA-matched donors. The stem cell source in eight patients was from siblings. Fourteen allogeneic transplant patients received RIST regimens. In the post-transplantation period, all patients were treated with immunosuppressive drug tacrolimus- or cyclosporine A-based regimens for prophylaxis of graft-versus-host disease (GVHD). Half of the patients were treated with tacrolimus and short-term methotrexate. The HCT-CI of most recipients was good.

3.3. Graft-versus-host disease and transplantation-related mortality

The cumulative incidences of grades II–IV acute and chronic GVHD were 41.7% and 72.8%, respectively. TRM for all patients was 25.0% at 100 days and 31.3% at 3 years (Fig. 1A). Regarding strategies, 3-year TRM was 12.5% in the front-line group and 50.0% in the salvage group (Fig. 1B). The outcome was unfavorable in the salvage group, but not significantly so (P = 0.19).

Table 2. Transplantation characteristics of patients (n = 16)

Characteristics	Value
Source	
Sibling/Unrelated	8/8 (50/50%)
HLA (Allele level)	
Matched	8 (50%)
1 mismatched	5 (31%)
2 mismatched	1 (6%)
3 mismatched	2 (13%)
Conditioning regimen	
Myeloablative	2 (12%)
Reduced-intensity conditioning	14 (88%)
Flu + L-PAM	9 (56%)
Flu + Cy + TBI	4 (25%)
L-PAM + TBI	2 (13%)
2CdA + Bu	1 (6%)
GVHD prophylaxis	
TAC-based	10 (63%)
CSP-based	6 (37%)
HCT-CI	
0	11 (69%)
1, 2	4 (31%)

HLA, human leukocyte antigen; Flu, fludarabine; L-PAM, melphalan; Cy, cyclophosphamide; TBI, total body irradiation; 2CdA, 2-chlorodeoxyadenosine; Bu, busulfan; GVHD, graft-versus-host disease; TAC, tacrolimus; CSP, cyclosporin A; HCT-CI, Hematopoietic Cell Transplant Co-morbidity Index.

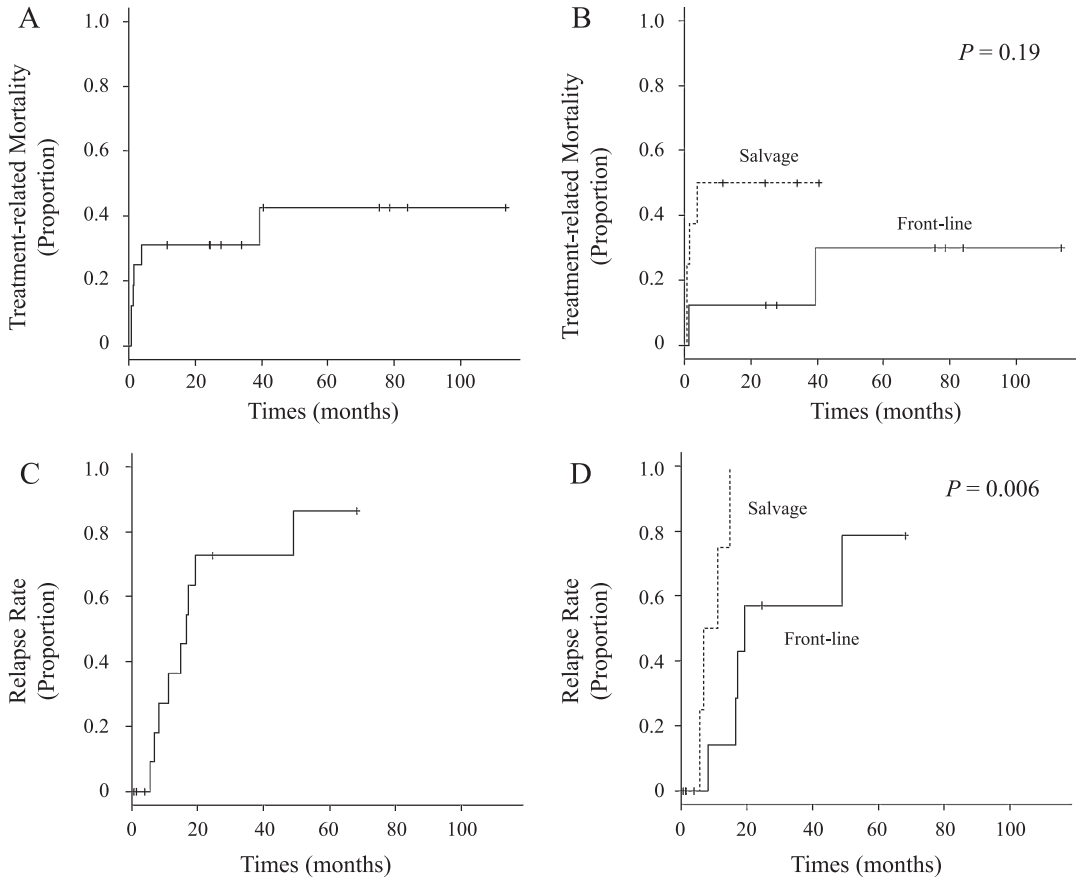

Figure 1. Cumulative incidence of TRM in all patients who underwent allo-SCT (A), and a comparison between front-line and salvage therapies (B). Cumulative incidence of RR in all patients who underwent allo-SCT (C), and a comparison between front-line and salvage therapies (D).

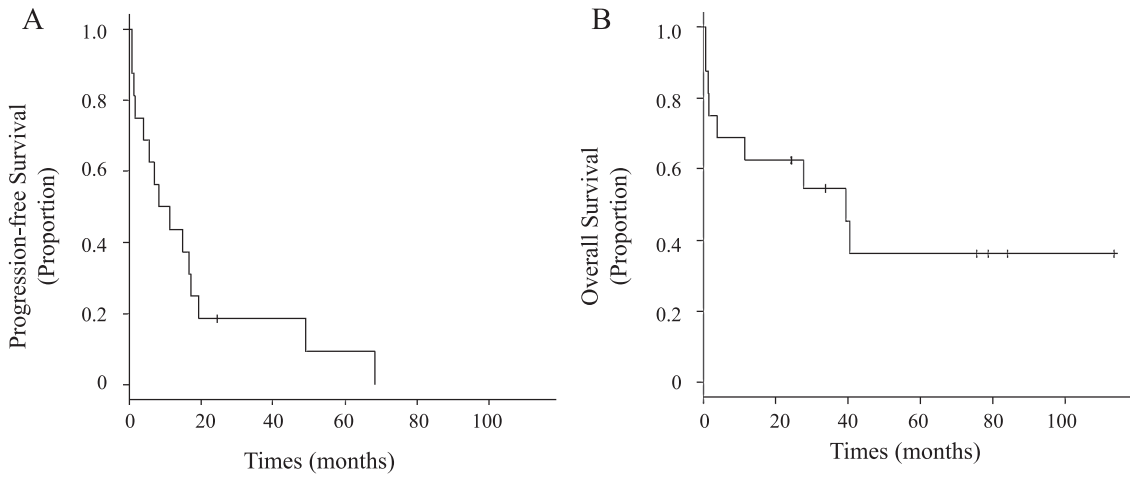

Figure 2. PFS (A) and OS (B) curves of 16 patients who underwent allo-SCT.

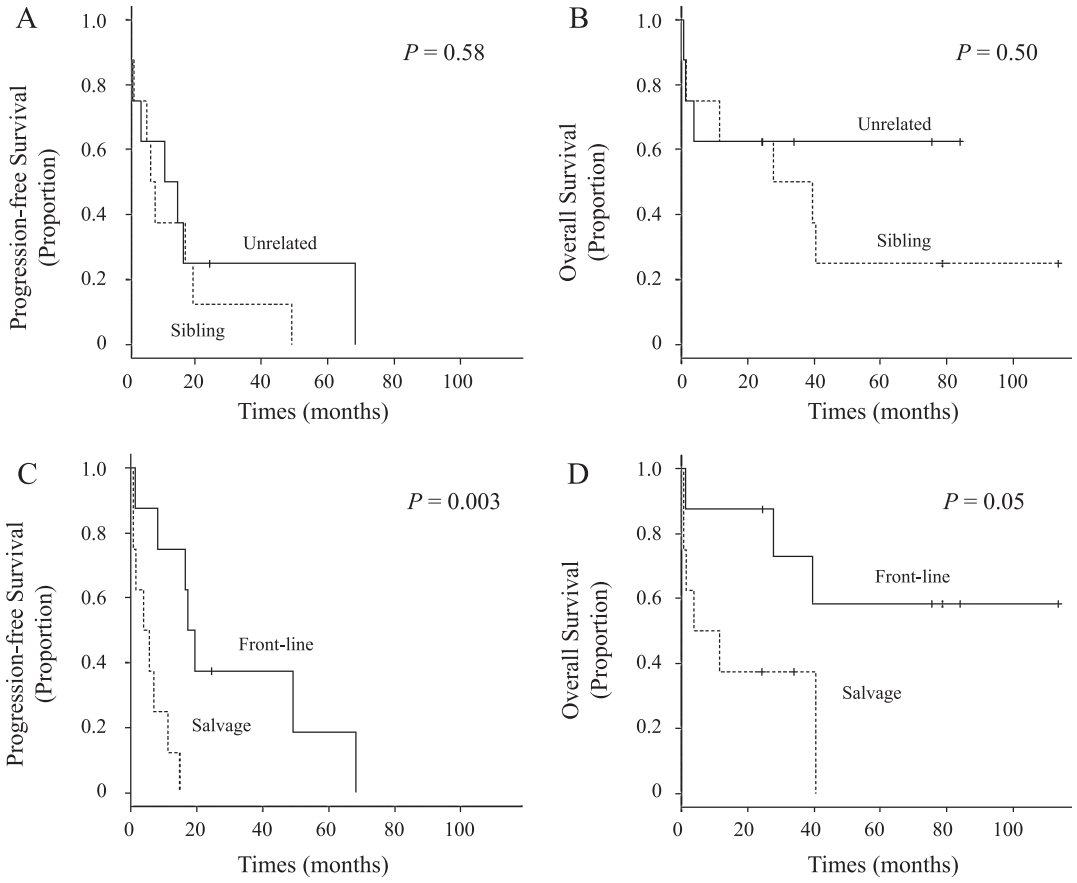

Figure 3. PFS (A) and OS (B) after allo-SCT are shown based on the donor type. PFS (C) and OS (D) after allo-SCT are also shown based on the treatment strategy.

3.4. Causes of death

Causes of death within 100 days after allo-SCT were multi-organ failure in 2 patients and sepsis, myocardial infarction, and graft failure in 1 patient each. After 100 days, bacterial pneumonia and obstructive bronchitis resulted in the death of 1 patient each. One patient died due to primary disease progression 8 months after allo-SCT. One patient relapsed 10 months after allo-SCT and, despite re-transplantation, had transplantation-related death.

3.5. Response after transplantation and survival

RR for all patients was 72.8% at 3 years (Fig. 1C). The 3-year RR in the front-line group (57.2%) was significantly lower than that in the salvage group (100.0%) (Fig. 1D, $P = 0.006$). In this

Table 3. Analysis of pretransplantation factors predicting overall survival

Factor	N	Hazard Ratio (95% CI)	*P*
Age at transplant			0.67
<50	9	1.00	
≥50	7	1.35 (0.35–5.27)	
Disease status at allo-SCT			0.03
Non-PD	9	1.00	
PD	7	4.73 (1.15–19.5)	
Strategy			0.06
Front-line	8	1.00	
Salvage	8	0.26 (0.06–1.08)	
Prior auto-SCT			0.10
No	8	1.00	
Yes	8	0.30 (0.07–1.27)	
Conditioning regimen			0.26
Myeloablative	2	1.00	
Reduced-intensity conditioning	14	0.38 (0.07–1.99)	
Source			0.51
Sibling	8	1.00	
Unrelated	8	0.62 (0.16–2.51)	
Donor			0.27
HLA-Matched	8	1.00	
HLA-mismatched	8	2.21 (0.55–8.88)	
Chronic GVHD			0.78
Yes	7	1.00	
No	4	1.38 (0.14–13.5)	

allo-SCT, allogenic stem cell transplantation; PD, progression disease; auto-SCT, autologous stem cell transplantation; HLA, human leukocyte antigen; GVHD, graft-versus-host disease.

study, the 3-year RR was high, even in the front-line group. Of the 10 patients with recurrence, 4 showed relapse as an extramedullary mass, which was controlled well by external radiation, and subsequently sustained CR over 1 year. One patient with recurrence was treated with lenalidomide, whereas the others did not receive new drugs such as bortezomib and immunomodulating drugs. The 4 patients with extramedullary relapse were all in the front-line group, and survived long-term, having a mean OS of 7.8 years.

The 3-year PFS in 16 patients with multiple myeloma was 18.8%, whereas the 3-year OS was 54.7% (Fig. 2A, B). No significant difference was observed between sources in either the 3-year PFS (12.5% for siblings vs 25% for unrelated donors; $P = 0.58$; Fig. 3A) or 3-year OS (50% for siblings vs 62.5% for unrelated donors; $P = 0.50$; Fig. 3B). The 3-year PFS was significantly higher in patients undergoing allo-SCT as front-line therapy than in those receiving transplantation as salvage therapy (37.5% in the front-line group vs 0% in the salvage group; $P = 0.003$; Fig. 3C). The 3-year OS was also significantly higher in the front-line group than in the salvage group (72.9% vs 37.5%; $P = 0.05$; Fig. 3D).

A univariate analysis was performed for various items including age at transplantation, disease status at allo-SCT, strategy, prior auto-SCT, conditioning regimen, stem cell source, HLA match, and chronic GVHD (Table 3). Only disease status at allo-SCT (non-PD vs PD) was significant (hazard ratio, 4.73; 95% confidence interval, 1.15–19.5; $P = 0.03$), whereas strategy (front-line vs salvage) showed a trend toward significance (hazard ratio, 0.26; 95% confidence interval, 0.06–1.08; $P = 0.06$). However, no significant difference in the other items was detected by this retrospective analysis because of the small number of patients.

4. Discussion

The indication of allo-SCT has been expanded since the RIST regimen was developed. Compared with other hematological diseases, multiple myeloma develops in older patients who cannot tolerate myeloablative conditioning. Previous studies reported that TRM and RR were both high in patients with multiple myeloma undergoing allo-SCT with myeloablative conditioning; therefore, this regimen has not been recommended in evidence-based medicine[4–6]. Several prospective studies have been conducted using RIST, which can reduce TRM, in patients with relapsed/refractory multiple myeloma[12–14]. TRM was improved, but remained high, ranging from 20% to 30%, and RIST did not result in an improvement in OS in relapsed/refractory multiple myeloma. New drugs such as bortezomib and immunomodulating drugs became available at around the same time. These drugs with low TRM have largely contributed to prolonged OS, leading to allo-SCT no longer being recommended as salvage therapy[15]. Our study also demonstrated the poor outcome of salvage therapy and was consistent with previous findings.

Some prospective studies used allo-SCT as front-line therapy for multiple myeloma[7,8]. Of particular interest are studies by groups from Sweden and Italy who performed auto-SCT followed by RIST on patients with *de novo* multiple myeloma. OS and PFS in these patients were both significantly higher than those in patients undergoing auto-SCT alone[7,8]. Furthermore, the outcomes achieved with auto-SCT followed by allo-SCT in front-line therapy were more favorable than those with salvage therapy[12–14]. However, TRM was still higher with this regimen than with auto-SCT alone[7,8]. Gahrton et al. also recently reported that long-term survival outcomes (8 years) after auto-SCT followed by RIST for new multiple myeloma were significantly better than those after auto-SCT alone[16]. TRM and RR were higher in the front-line group in our study, whereas OS was similar to the findings reported by these two groups. Our results also revealed some long-term survivors of multiple myeloma in the front-line group, which suggest that those

who underwent allo-SCT as front-line therapy had markedly better prognoses.

More patients can achieve CR before auto-SCT due to the development of new drugs. A previous study showed that patients achieving CR before auto-SCT were more likely to have improved prognoses[3]. In addition, Crawley et al.[17] reported that CR/VGPR/PR, but not PD, prior to RIST was associated with improved OS. In our study, a univariate analysis for disease status also revealed that myeloma patients with PD were not expected to have prolonged OS, which was consistent with previous findings. Allo-SCT may only be effective for myeloma patients with a well-controlled disease status. Serum-free light chain analyses have enabled the detailed evaluation of disease statuses[18]. Therefore, the identification of stringent CR by this analysis will be of importance in the success of allo-SCT.

Greater difficulties are associated with obtaining the graft-versus-myeloma (GVM) effect in multiple myeloma than in other hematological malignancies[4,5]. Previous studies reported that patients with multiple myeloma had higher RR than those with other diseases. On the other hand, patients with chronic GVHD were shown to have a reduced risk of recurrence, which indicated the presence of the GVM effect, and there was no contribution to extended OS[19–21]. Although the presence of chronic GVHD in this study did not contribute to prolonged OS, some recurrent cases had an extramedullary mass, which was controlled well by external radiation, and subsequently sustained CR over 1 year. A chimerism analysis at the onset of recurrence showed a full donor-cell population, which supported the GVM effect being expected in bone marrow. Hereafter, longer survival can be expected in our recurrent patients receiving new drugs such as bortezomib and immunomodulating drugs. Our results showed that only disease status at allo-SCT (non-PD vs PD) was significant, whereas strategy (front-line vs salvage) showed a trend for significance for overall survival. However, no significant difference was detected in the other items by this retrospective analysis because of the small number of patients.

Multiple myeloma is currently very hard to cure with new drugs and/or auto-SCT. Furthermore, the findings of previous studies and the results of the present study demonstrated that allo-SCT is not desirable as salvage therapy. New drugs have improved the treatment options for myeloma patients; therefore, allo-SCT remains a controversial treatment because of high RR and TRM. In our study, some patients who underwent allo-SCT as front-line therapy without maintenance survived as long as those in a previous study[16]. This result suggests that the GVM effect contributed, at least in part, to disease control.

According to our study, the OS and PFS recieved allo-SCT were not superior to those recieved more common therapies, such as autologous stem cell transplantation or combined chemotherapy with new agents. We need to have more progress in allo-SCT for MM while establishing safe and effective procedures.

5. Conflicts of Interest Disclosures

The authors declare no competing financial interests related to this work.

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