**Introduction**

Allogeneic hematopoietic stem cell transplantation (allo-SCT) is the only potentially curative treatment for patients with plasma cell myeloma (PCM), and has been performed since the early 1980s.\(^1\) Regarding the intensity of conditioning for the transplant, allo-SCT with myeloablative conditioning was usually used until the late 1990s. Since then, myeloablative conditioning has been less commonly used because of its high incidence of treatment-related mortality (TRM), ranging from 30% to 60%.\(^2\)-\(^4\)

The tandem approach of autologous stem cell transplantation (ASCT) followed by non-myeloablative allografting became widely used in the early 2000s.\(^5\),\(^6\) The
rationale for this tandem approach is the separation in time between tumor reduction with high-dose chemotherapy and the graft-versus-myeloma effect with allografting. Indeed, the combination of ASCT followed by reduced-intensity conditioning (RIC) allo-SCT has significantly reduced the incidence of TRM, to 20% or less. However, the benefit of RIC allo-SCT in PCM remains controversial due to the lack of evidence that RIC allo-SCT improves the prognosis of PCM patients compared with single or double ASCT or ASCT combined with recently developed agents. Accordingly, RIC allo-SCT has generally been considered an optional treatment for relapsed PCM patients after treatment with ASCT.

In this article, we report our single-center retrospective analysis of RIC allo-SCT for 10 patients with PCM. Our results suggest that RIC allo-SCT is beneficial for PCM patients in disease remission in the early period after the diagnosis.

Patients and Methods

Patient characteristics

From March 2001 to July 2006, 10 patients underwent RIC allo-SCT at Kyoto University Hospital according to protocols approved by the institutional review boards of the Graduate School of Medicine, Kyoto University. The number of patients undergoing allo-SCT at this hospital had declined substantially with the emergence of some novel agents, and no patient had received RIC allo-SCT according to this protocol since 2007. Data were collected and updated as of November 2011.

The patient inclusion criteria of the protocol were: aged 16–69 years, performance status 0–2, adequate organ function, no extramedullary plasmacytoma, and no uncontrolled infection.

The clinical characteristics of the 10 patients are shown in Table 1. The median follow-up period was 90 months after RIC allo-SCT. The median age of these patients at the time of allo-SCT was 51 years, ranging from 35 to 65. Regarding the immunoglobulin isotype of the M-protein, 7, 2, and 1 patient had IgG, light chain, and IgA types, respectively. According to the Durie-Salmon staging system at the time of diagnosis, 8 patients were in stage III, and 2 were in II. Serum-2 microglobulin levels were greater than 3.5 mg/L at the time of diagnosis in 6 patients.

A cytogenetic analysis of myeloma cells was performed in 8 patients using bone marrow samples: high-risk cytogenetic aberration as defined by del(13q) by metaphase karyotyping and t(4; 14) and/or del(17p) by interphase fluorescent in situ hybridization (FISH) analysis was detected in only one patient (no. 9) who carried a complex karyotype involving del(13q) by analysis of G-banded chromosomes. A FISH analysis showed that two other patients (nos. 5, 6) carried del(13q), and one patient (no. 1) carried t(11; 14).

A total of 5 patients (nos. 1, 3, 4, 5, and 9) received RIC allo-SCT as an upfront consolidation after ASCT conditioned with high-dose melphalan: 3 achieved a complete response (CR) and 2 achieved a partial response (PR) before RIC allo-SCT. The median time from ASCT to allo-SCT was 3.7 months (range: 3.3–5.1 months) in these 5 patients. Another 4 patients (nos. 2, 6, 7, and 10) received RIC allo-SCT as a salvage treatment for disease progression after the initial ASCT. The remaining patient (no. 8) was refractory to several types of standard-dose chemotherapy, and received RIC allo-SCT as a salvage consolidation after repeated high-dose chemotherapy followed by ASCT.

RIC allo-SCT

All 10 patients received a fludarabine-based RIC regimen as the conditioning before allo-SCT (Table 2). The regimen consisted of fludarabine (125 mg/m²), busulfan (8 mg/kg), and total body irradiation (TBI) of 2 or 4 Gy in 8 patients, fludarabine (125 mg/m²) and busulfan (8 mg/kg) in 1 patient, and fludarabine (125 mg/m²) and melphalan (140 mg/m²) in the remaining patient. The stem cell source was bone marrow (BM) from an HLA-matched related donor in 2 patients, peripheral blood stem cells from an HLA-matched related donor in 5, BM from an HLA-matched unrelated donor in 2, and HLA two locus-mismatched cord blood in 1 patient. Seven patients with an HLA-matched related donor received graft-versus-host disease (GVHD) prophylaxis with tacrolimus and short-term methotrexate (MTX). The dosage of tacrolimus was adjusted to serum concentration level of 10–15 ng/ml. MTX 5 mg/m² was given on days 1, 3, and 6 after allo-SCT. Mycophenolate mofetil was added for the two patients who received their transplant from an HLA-matched unrelated donor. The remaining patient, who underwent a cord blood transplant, received tacrolimus only. In all patients, no additional treatment for PCM was performed after allo-SCT until disease progression.
Table 1. Patient characteristics and treatment prior to allo-SCT

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Gender</th>
<th>Age at allo-SCT</th>
<th>Immunologic subtype</th>
<th>Durie-Salmon/ISS stage at Dx</th>
<th>Serum-β2m at Dx (mg/l)</th>
<th>Treatment prior to allo-SCT</th>
<th>Disease status at allo-SCT</th>
<th>Time from Dx to allo-SCT (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>52</td>
<td>LC</td>
<td>III A/2</td>
<td>4.1</td>
<td>VAD ⇒ ASCT</td>
<td>1st remission (PR)</td>
<td>8.9</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>52</td>
<td>IgG</td>
<td>III A/2</td>
<td>2.5</td>
<td>VAD ⇒ ASCT × 2 ⇒ IFN ⇒ hyper CVAD</td>
<td>1st relapse</td>
<td>25.1</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>51</td>
<td>IgA</td>
<td>III A/3</td>
<td>16.23</td>
<td>VAD ⇒ ASCT</td>
<td>1st remission (CR)</td>
<td>9.2</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>54</td>
<td>LC</td>
<td>III A/3</td>
<td>5.5</td>
<td>VAD ⇒ ASCT</td>
<td>1st remission (CR)</td>
<td>8.0</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>46</td>
<td>IgG</td>
<td>III A/2</td>
<td>3.6</td>
<td>VAD ⇒ ASCT</td>
<td>1st remission (CR)</td>
<td>9.1</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>65</td>
<td>IgG</td>
<td>III A/1</td>
<td>2.2</td>
<td>MP, VAD ⇒ ASCT ⇒ IFN ⇒</td>
<td>1st relapse</td>
<td>46.2</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>51</td>
<td>IgG</td>
<td>III A/2</td>
<td>2.2</td>
<td>VAD ⇒ ASCT ⇒ IFN</td>
<td>1st relapse</td>
<td>62.3</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>35</td>
<td>IgG</td>
<td>III A/1</td>
<td>2.3</td>
<td>VAD, VCR + MCNU + DEX ⇒</td>
<td>Refractory</td>
<td>24.9</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>41</td>
<td>IgG</td>
<td>III A/2</td>
<td>4.8</td>
<td>VAD ⇒ ASCT</td>
<td>1st remission (PR)</td>
<td>9.6</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>35</td>
<td>IgG</td>
<td>III A/2</td>
<td>3.6</td>
<td>VAD ⇒ DCEP ⇒ ASCT ⇒</td>
<td>1st relapse</td>
<td>20.2</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; CVAD, cyclophosphamide+vincristine+doxorubicin+dexamethasone; DCEP, dexamethasone+cyclophosphamide+etoposide+cisplatin; DEX, dexamethasone; Dx, diagnosis; IFN, interferon; ISS, international staging system; LC, light chain; MCNU, ranimustine; MP, melphalan+predonisolone; MTD, melphalan+thalidomide+dexamethasone; ROAD, ranimustine+vincristine+doxorubicin+dexamethasone; TD, thalidomide+dexamethasone; VAD, vincristine+doxorubicin+dexamethasone; VCR, vincristine.

Table 2. Transplant-related events and outcomes after allo-SCT

<table>
<thead>
<tr>
<th>Case no.</th>
<th>RIC regimen</th>
<th>Donor/Stem cell source</th>
<th>GVHD prophylaxis</th>
<th>aGVHD</th>
<th>cGVHD</th>
<th>Best response after allo-SCT</th>
<th>Outcome</th>
<th>Follow-up period since allo-SCT (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FLU-Mel</td>
<td>MRD/BM</td>
<td>FK506 + MTX</td>
<td>II</td>
<td>Limited</td>
<td>CR</td>
<td>Alive/CR</td>
<td>125.7 +</td>
</tr>
<tr>
<td>2</td>
<td>FLU-BU</td>
<td>MRD/PBSC</td>
<td>FK506 + MTX</td>
<td>II</td>
<td>Extensive</td>
<td>CR</td>
<td>Died of GVHD and infection</td>
<td>4.4</td>
</tr>
<tr>
<td>3</td>
<td>FLU-BU-TBI</td>
<td>MRD/BM</td>
<td>FK506 + MTX</td>
<td>II</td>
<td>Limited</td>
<td>CR</td>
<td>Alive/Relapsed</td>
<td>101.8 +</td>
</tr>
<tr>
<td>4</td>
<td>FLU-BU-TBI</td>
<td>MRD/PBSC</td>
<td>FK506 + MTX</td>
<td>II</td>
<td>Extensive</td>
<td>CR</td>
<td>Alive/CR</td>
<td>101.5 +</td>
</tr>
<tr>
<td>5</td>
<td>FLU-BU-TBI</td>
<td>MRD/PBSC</td>
<td>FK506 + MTX</td>
<td>II</td>
<td>Limited</td>
<td>CR</td>
<td>Alive/CR</td>
<td>98.3 +</td>
</tr>
<tr>
<td>6</td>
<td>FLU-BU-TBI</td>
<td>MRD/PBSC</td>
<td>FK506 + MTX</td>
<td>I</td>
<td>Extensive</td>
<td>CR</td>
<td>Died of PD</td>
<td>23.3</td>
</tr>
<tr>
<td>7</td>
<td>FLU-BU-TBI</td>
<td>MUD/BM</td>
<td>FK506 + MTX + MMF</td>
<td>II</td>
<td>Extensive</td>
<td>CR</td>
<td>Died of PD</td>
<td>29.5</td>
</tr>
<tr>
<td>8</td>
<td>FLU-BU-TBI</td>
<td>MUD/BM</td>
<td>FK506 + MTX + MMF</td>
<td>no</td>
<td>Limited</td>
<td>CR</td>
<td>Alive/Relapsed</td>
<td>95.3 +</td>
</tr>
<tr>
<td>9</td>
<td>FLU-BU-TBI</td>
<td>MRD/PBSC</td>
<td>FK506 + MTX</td>
<td>no</td>
<td>Limited</td>
<td>CR</td>
<td>Alive/Relapsed</td>
<td>84.4 +</td>
</tr>
<tr>
<td>10</td>
<td>FLU-BU-TBI</td>
<td>2 mismatched-CB</td>
<td>FK506</td>
<td>II</td>
<td>Not evaluable</td>
<td>PD</td>
<td>Died of PD</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Abbreviations: BM, bone marrow; BU, busulfan; CB, cord blood; FK506, tacrolimus; FLU, fludarabine; Mel, melphalan; MMF, mycophenolate mofetil; MRD, matched-related donor; MUD, matched unrelated donor; MTX, methotrexate; PBSC, peripheral blood stem cell.
Assessment of clinical outcomes and statistical analysis

CR was defined by the absence of detectable M-protein in the serum and urine by immunofixation. Very good partial response was defined as serum and urine M-protein detectable by immunofixation but not by electrophoresis, or at least a 90% reduction in serum M-protein, and urine M-protein <100 mg/24 hours. PR was defined as a more than 50% reduction in the concentration of serum M-protein and more than 90% reduction in the amount of urinary M-protein. Overall survival (OS) was determined from the date of allo-SCT to that of death from any cause or to the last follow-up date. Progression-free survival (PFS) was determined from the date of allografting to that of documented disease progression. The survival curves were calculated according to the Kaplan-Meier method.

Results

Engraftment and GVHD

All 10 patients achieved the engraftment of neutrophils, platelets, and reticulocytes. Seven patients developed grade II–III acute GVHD (aGVHD) and none developed grade IV aGVHD (Table 2). Chronic GVHD (cGVHD) was evaluable in 9 patients. Five patients developed limited cGVHD, and 4 developed extensive cGVHD. Patients with grade III aGVHD (nos. 1 and 2) or extensive cGVHD (nos. 2, 4, 6, and 7) were treated with prednisolone (1–2mg/kg/day). In 4 of these 5 patients (no. 2 excluded), GVHD was promptly relieved with steroid treatment. In patient no. 2, chronic pulmonary GVHD was exacerbated and steroid-pulse therapy was administered, but was not effective, resulting in the patient’s death due to adenovirus infection.

Outcomes after allo-SCT

Two patients (nos. 2 and 10) died within 1 year after allo-SCT: one from systemic adenovirus infection on day 135 and the other from progressive disease on day 148. All 8 evaluable patients achieved a CR after allo-SCT, and, thereafter, PCM recurred in 5 of the 8 patients. The median time to relapse after allo-SCT was 22 months (range: 11–48 months). Two patients (nos. 6 and 7) died of progressive disease at 23 and 30 months after allo-SCT, respectively. At the time of the last follow-up, 6 of the total 10 patients were alive, 3 (nos. 1, 4, and 5) without recurrence and 3 (nos. 3, 8, and 9) with recurrent disease. The 3 relapsed patients, whose median follow-up period was 95 months (range: 84–102 months) after allo-SCT, are currently in a stable disease state with novel agents and/or salvage chemotherapy. All of the 6 survivors showed a good performance status (Karnofsky PS: 90% in 1 patient, 100% in 5) at the time of the last follow-up. The 5-year OS was 69%, and the PFS was 34% at 90 months of median follow-up after allo-SCT (Fig. 1).

Discussion

This was a retrospective study of 10 PCM patients who underwent fludarabine-based RIC allo-SCT in our institution. After a median follow-up of more than 7 years, there were 6
long-term survivors, 3 of whom have shown a CR for up to 8 years without maintenance therapy. The other 3 patients showed relapsed disease between 18 and 49 months after allo-SCT, and were alive with stable disease on treatment with novel agents, including thalidomide, lenalidomide, and bortezomib. Five of the 6 long-term survivors had received allo-SCT from an HLA-matched related donor during the first remission within 10 months after the initial diagnosis. On the other hand, all 4 patients who received allo-SCT with relapsed disease after ASCT died of transplant-related toxicity or progressive disease between 4 and 30 months after allo-SCT. Encouraging results were obtained, particularly in the patients who received RIC allo-SCT during their first remission after ASCT.

Similar results have been shown in previous studies. Two large series from Seattle and Italy reported on more than 200 PCM patients who received a single ASCT followed by RIC allo-SCT (tandem auto-/allo-SCT).5,6 The Seattle group reported that the 5-year OS and PFS were 64% and 36%, respectively. The Italian group showed that, after a median follow-up of 5 years, the median OS was not reached and event-free survival (EFS) was 37 months.

Studies of RIC allo-SCT for relapsed or refractory myeloma patients have provided additional OS and PFS data. Yvonne et al. reported that the 2-year OS and PFS were 32% and 19%, respectively.13 Similarly, the EBMT (European Group for Blood and Marrow Transplantation) study described an estimated 5-year OS and PFS of 26% and 20%, respectively.14

At our institution, 17 PCM patients underwent single or double ASCT after initial induction chemotherapy in our institution between 2001 and 2006, and 8 of them received maintenance therapy with interferon or thalidomide after the ASCT. After a median follow-up of 83 months, there were 3 long-term survivors, only one of whom remains alive without recurrence.

However, allo-SCT as part of first-line therapy should be offered to PCM patients only in the context of clinical trials, because some prospective studies showed no significant advantage in survival after non-myeloablative allo-SCT following ASCT compared with double ASCT.8-10 Four large prospective trials comparing the combination of ASCT followed by RIC allo-SCT with tandem ASCT have been reported.7-10 Only one trial (from the Italian group) showed that both the OS and EFS were significantly longer in patients who received tandem auto-/allo-SCT than in patients who underwent tandem ASCT.7 The four trials’ different study designs including the inclusion criteria, conditioning regimen, and GVHD prophylaxis method may explain the differing results among the trials.

Regarding the conditioning regimens of the four trials,7-10 the American group10 (BMT CTN 0102) and the Italian group7 used 2 Gy TBI before allo-SCT. In the French (IFM99–03)8 and Spanish (PETHEMA)9 trials, the conditioning regimen consisted of fludarabine, busulfan and antithymocyte globulin (ATG), and fludarabine and melphalan (140 mg/m²), respectively.8,9 The conditioning regimens using 2 Gy TBI may have significantly reduced the TRM, but probably decreased the curative potential of allo-SCT. The preparative regimen including high-dose ATG, which was used by the French group, might have inhibited the graft-versus-myeloma (GVM) effect. The conditioning regimen in the Spanish group trial resulted in a significantly longer PFS but higher TRM compared to the regimens in the other three trials.

In the present study, we used a conditioning regimen of fludarabine, busulfan, and low-dose TBI in 8 of the 10 patients. Only one patient, who had received repeated high-intensity chemotherapy before the RIC allo-SCT, died of TRM. All evaluable patients developed cGVHD, and all six of the long-term survivors maintained a favorable performance status. Accordingly, our preparative regimen may be less toxic and may induce a potent GVM effect, although the number of patients is too small to draw definite conclusions. Identifying an optimal conditioning regimen will make it possible to improve the long-term prognosis of patients undergoing allo-SCT.

In addition, it is necessary to identify markers which could predict myeloma patients who are more likely to be benefit from RIC allo-SCT. As identified in the IFM99–038 and BMT CTN 010210 trials, the risk factors defined by the serum β2-microglobulin level and abnormality of chromosome 13 could not predict the benefit of allo-SCT. To the best of our knowledge, no prospective study has ever been conducted comparing tandem auto-/allo-SCT with tandem ASCT for high-risk patients in relation to other chromosomal abnormalities including t(4; 14), t(14; 16), or del(17p), although some retrospective analyses suggested a potential benefit of first-line allo-SCT in high-risk populations.15,16 In the present study, cytogenetic analysis was performed in two of the three non-relapsed survivors. No poor prognostic cytogenetic abnormalities, such as t(4; 14), del(17p), or t(14;
16), were detected using both conventional G-banding and FISH analysis in these two patients. This result may indicate that patients without high-risk cytogenetic abnormalities are more likely to benefit from RIC allo-SCT, although the number of patients was too small in the present study to draw any definite inference.

In conclusion, our results suggest that RIC allo-SCT has the potential to facilitate long-term progression-free survival in patients with PCM in first remission after upfront autologous transplantation. An approximately ten-year progression-free survival without additional therapy after allo-SCT for PCM would represent a marked improvement of both the quality of life of PCM patients and the cost-effectiveness of allo-SCT. RIC allo-SCT for PCM might be a treatment of choice within the well designed trial, especially in the early period after diagnosis, if an HLA-matched related donor is available. We should challenge to perform the prospective studies of allo-SCT with fludarabine-based RIC for PCM patients in first remission after induction therapy including novel agents and ASCT, in order to achieve a cure for patients with PCM.

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Authors’ contributions: MM and TK designed the study, analyzed the data, and wrote the manuscript; MH, MN, KY, TI, NK, TI and AT-K analyzed data and approved the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

References


