ORIGINAL ARTICLE

Allo-SCT for multiple myeloma: a review of outcomes at a single transplant center

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INTRODUCTION

The survival of patients with multiple myeloma (MM) has improved over the last decade as a result of melphalan-based high-dose therapy followed by auto-SCT, the introduction of novel anti-myeloma agents with increased efficacy in relapsed and refractory MM, and improvements in supportive care.\(^1\)\(^-\)\(^6\) Registry data indicate an improvement in median survival from 3 to 5 years, primarily among younger patients, as a result of these treatment innovations.\(^7\) Despite these new developments, MM remains an incurable disease for the large majority, as all but a few patients will relapse. Allogeneic hematopoietic cell transplantation is currently one treatment with a potential for long-term disease control although its curative potential is debated. This is in part due to the graft-vs-myeloma effect, mediated by immune competent donor lymphocytes, best illustrated by the induction of sustained (molecular) remissions following donor lymphocyte infusions,\(^8\) but could also be due in part to absence of contaminating myeloma cells in the donor graft and documented lower levels of residual disease.\(^9\)\(^,\)\(^10\)

The role of allo-SCT in MM, however, is controversial due to the high mortality and morbidity associated with conventional myeloablative regimens and because convincing evidence for a survival benefit is lacking.\(^11\)\(^-\)\(^13\) In the last decade, non-myeloablative allo-SCT has gained in popularity due to significantly less acute GVHD, lower transplant mortality, better PFS and overall survival. There were no significant differences in relapse, progression or chronic GVHD, when adjusted. In multivariable analysis of patients receiving only non-myeloablative transplants, decreased overall survival and PFS were associated with relapse after a prior autograft and a β2 microglobulin > 4.0. Transplant mortality was reduced and only influenced by a prior tandem autograft. Furthermore, at least one registry report comparing conventional ablative with non-myeloablative/reduced intensity allo-SCTs have shown similar survival outcomes with lower TRM for patients receiving non-ablative transplants yet higher rates of relapse and PFS inferior to ablative allo-SCT.\(^21\) We reviewed our results of allo-SCT for patients with MM beginning in 1975 with the aim of identifying factors associated with improvements in disease-free survival and OS as preparative regimens have changed from ablative to non-myeloablative.

PATIENTS AND METHODS

Beginning in 1975, patients with MM were referred to the University of Washington, Fred Hutchinson Cancer Research Center or the Seattle Veterans Hospital for consideration of allo-SCT. Patients were evaluated for suitability for transplant based on treatment protocols in effect at the time. Patient records, laboratory, X-rays and marrow aspirates were reviewed to confirm the diagnosis of MM. To be considered for marrow transplantation, patients had to meet the established criteria for active, symptomatic MM according to Durie and Salmon\(^22\) and had to have received at least one cycle of conventional dose chemotherapy. Patients with a Karnofsky score of < 50, a pulmonary diffusion capacity of < 50% of predicted and symptomatic heart failure were excluded. Non-ablative transplant candidates were allowed to enroll with a diffusion capacity as low as 30%. Standard hematologic and chemistry studies were used to evaluate organ function. A suitable marrow donor was required, which included HLA identical relatives, HLA haplo-identical relatives or an unrelated donor who was phenotypically HLA identical, or single allele or Ag HLA-mismatched at class I with the patient. Transplants occurred between January 1975 and September 2008. The date of last follow-up was August 2011.

Initially, patients who had achieved a complete response (CR) to first-line therapy and were without any evidence of disease were excluded from transplantation. This policy changed, however, as non-myeloablative...
allo-SCT regimens were adopted. Ablative allo-SCT were utilized as stand-alone therapy. In contrast, non-ablative allo-SCT were performed in the majority of patients, 2–4 months following recovery from a standard auto-SCT utilizing high-dose melphalan. The auto-SCT was utilized to provide cyto-reduction before the non-ablative allo-SCT, yet allow the patient time to recover from the effects of high-dose therapy used for auto-SCT. Maintenance therapies were not used following allo-SCT.

For purposes of this analysis, patients with at least a 50% reduction in monoclonal proteins in the blood or a 75% reduction in 24 h quantitative Bence Jones protein, to their most recent chemotherapy before allo-SCT or auto-SCT, in the case of tandem transplants, were categorized as having sensitive disease, whereas all other patients were judged to have chemotherapy-resistant disease.

Responses were categorized according to the IMWG criteria.23 If certain data were missing that were required for response categorization, for example immunofixation for CR, the patient was classified as responding in the next lower category. An analysis of OS, PFS, TRM, relapse or progression, acute and chronic GVHD was undertaken. The initial analysis compared outcomes using non-myeloablative conditioning for the allogeneic transplant vs those with myeloablative conditioning. In the analysis of relapse or progression, time-dependent competing risks of treatment failure such as death from TRM were included. Cox regression models for these outcomes were adjusted for patient age (continuous), donor sex, chemotherapy responsive vs resistant disease, related vs unrelated donor, time from diagnosis to transplant (<2.5 years vs >2.5 years), prior radiation, prior number of chemotherapy regimens (continuous), beta-2 microglobulin levels, albumin and cytogenetic data were limited. A higher percentage of patients receiving ablative regimens had been given local radiation therapy, 50% compared with patients receiving non-ablative regimens, 33%. One third of the patients receiving non-ablative conditioning had progressed after an autologous transplant, while only four patients receiving ablative conditioning had progressed after an autologous transplant. A higher percentage of patients receiving ablative regimens were judged to have refractory disease, 77%, (based on less than a partial response to their last salvage chemotherapy), compared with 52% of patients who received non-ablative regimens. Relatively few patients were in remission before allografting; two patients undergoing myelo-

### RESULTS

Patient characteristics are shown in Table 1. Patients receiving non-myeloablative allo-SCTs were older by a median of 8 years. There were no important differences in the percentages of patients with advanced Durie Salmon staging, IgG or IgA subtypes, number of prior regimens, or total cycles of chemotherapy. Availability of data on beta-2 microglobulin levels, albumin and cytogenetic data were limited. A higher percentage of patients receiving ablative regimens had been given local radiation therapy, 50% compared with patients receiving non-ablative regimens, 33%. One third of the patients receiving non-ablative conditioning had progressed after an autologous transplant, while only four patients receiving ablative conditioning had progressed after an autologous transplant. A higher percentage of patients receiving ablative regimens were judged to have refractory disease, 77%, (based on less than a partial response to their last salvage chemotherapy), compared with 52% of patients who received non-ablative regimens. Relatively few patients were in remission before allografting; two patients undergoing myelo-

### Table 1. Patient and treatment characteristics

| Characteristics                  | All patients | Myeloablative | Non-myeloablative |
|----------------------------------|--------------|---------------|-------------------|
| No. of patients                  | 278          | 144           | 134               |
| Date of first transplant         | January 1975 | January 1975  | March 1998        |
| Sex, % male                      | 63           | 62            | 64                |
| Age, median (range)              | 49 (20–69)   | 45 (20–59)    | 53 (25–69)        |
| % Durie salmon stage3            | 77           | 79            | 75                |
| Type                             |              |               |                   |
| IgG                              | 156          | 80            | 76                |
| IgA                              | 64           | 31            | 33                |
| Light chain                      | 39           | 24            | 15                |
| Nonsecretory                     | 13           | 5             | 8                 |
| IgD                              | 2            | 1             | 1                 |
| IgM                              | 1            | 1             |                   |
| Plasma cell leukemia             | 7            | 4             | 3                 |
| B-2m                             |              |               |                   |
| At dx (n = 19)                   | 4.1 (1.3–14.6)| 2.9 (0.8–24.4), n = 52 | 1.8 (0.8–10.3), n = 70 |
| At tx (n = 122)                  |              |               |                   |
| Albumin at tx (n = 236)          | 3.5 (1.4–4.9)| 3.5 (1.4–4.9), n = 118 | 3.5 (2.0–4.4), n = 118 |
| Cytogenetics                     |              |               |                   |
| Normal                          | At dx 0, at tx 53 | At dx 15, at tx 96 |
| Abnormal                        | At dx 2, at tx 9 | At dx 18, at tx 12 |
| FISH any abnormality             |              |               |                   |
| Prior radiation                  | 11           | 30            |                   |
| No. of regimens                  | 72           | 44            |                   |
| Total chemotherapy cycles        | 2 (1–6)      | 2 (1–6)       |                   |
| Tandem auto-allo (%)             | 0            | 99 (74)       |                   |
| Relapse after autograft (%)      | 4            | 46 (34)       |                   |
| Refractory (%)                   | 65           | 77            | 52                |
| Survivors follow-up, median years| 15.1 (3.6–23.5)| 1.5 (0.3–11.4)| 7.1 (2.9–12.9)    |

2Includes hyperdiploidy, numbers at dx = diagnosis, at tx = transplant. 3Refractory patients achieved <PR to their last salvage therapy prior to allograft or tandem auto-allograft.
The majority of regimens for GVHD prophylaxis in ablative recipients consisted of a calcineurin inhibitor with MTX or steroids. Almost all recipients of non-ablative regimens received a calcineurin inhibitor and mycophenolic acid for GVHD prophylaxis.

Response to transplant
Among the 144 ablative transplant recipients, 33 (23%) achieved CRs, 33 (23%) a partial response, 12 (8%) did not respond and 67 (46%) were not evaluable owing to early death. Of 134 patients receiving non-ablative transplants, 51 (38%) achieved a CR, 48 (36%) a partial response, 31 (23%) did not respond, whereas 4 (3%) were not evaluable owing to early death. Patients who achieved a CR (n = 84) had 5 and 10 year survivals of 62 and 53% compared with patients who did not achieve a CR (n = 132) and excluding patients who were not evaluable owing to early death, who had 5 and 10 year survivals of 28% and 17%, respectively.

Among patients who received ablative conditioning, 104 developed acute GVHD; 7 grade 1, 44 grade 2, 34 grade 3 and 19 grade 4. Of patients who received non-ablative conditioning acute GVHD occurred in 90; grade 1 in 6, grade 2 in 72, grade 3 in 8 and grade 4 in 4. The cumulative incidences of chronic extensive GVHD were 27% and 66% for patients receiving ablative and non-ablative conditioning regimens, respectively.

Cox regression analysis of overall mortality, PFS, TRM, relapse or progression and acute or chronic GVHD between non-myeloablative and ablative regimens are shown in Table 4. When adjusted for patient and donor factors, non-myeloablative conditioning resulted in significantly lower overall mortality HR 0.40 (0.3 - 0.6), improved PFS HR 0.55 (0.4 - 0.8) and much lower TRM HR 0.22 (0.1 - 0.4). The risks of acute GVHD grades 2 - 4 were also significantly lower with non-myeloablative regimens HR 0.41 (0.3 - 0.6). The risks of relapse or progression and chronic GVHD when adjusted for competing risks of death and patient and donor factors, were not significantly different between ablative and non-ablative conditioning, despite the almost exclusive use of PBSCs for the non ablative recipients.

In a separate multivariable analysis, outcomes of only patients undergoing non-ablative allogeneic transplants were considered. (Table 5) The most important predictors of survival, PFS and TRM were donor factors, type of conditioning regimen and myelosuppression.

### Table 2. Patient treatment characteristics

| Characteristics                  | All patients | Myeloablative | Non-myeloablative |
|----------------------------------|--------------|---------------|-------------------|
| No. of patients                  | 278          | 144           | 134               |
| Conditioning regimens            |              |               |                   |
| 2 Gy TBI                         | 64           | 16            | 1                 |
| Fludarabine, 2 Gy TBI            | 54           | 44            | 1                 |
| L-PAM, fludarabine               | 14           | 18            | 6                 |
| 2 Gy TBI                         |              | 2             |                   |
| CY, fludarabine, 2 Gy TBI        | 2            | 1             |                   |
| Holmium, fludarabine             | 1            |               |                   |
| 2 Gy TBI                         |              | 1             |                   |
| CY, 12 Gy TBI                    | 16           | 1             |                   |
| L-PAM, 12 Gy TBI                 | 1            | 8             |                   |
| BU, CY, modified TBI 9 Gy        | 44           | 38            | 7                 |
| BU, modified TBI 9 - 12 Gy       | 8            |               |                   |
| BU, CY                           | 69           | 67            | 2                 |
| BU, L-PAM                        | 3            |               |                   |
| BEAM                             | 1            |               |                   |
| DMM, Etoposide, 10 Gy TBI        | 1            |               |                   |
| Donors                           |              |               |                   |
| Sibling-matched                  | 110          | 88            | 2                 |
| Sibling-haploidentical           | 4            |               |                   |
| Parent-haploidentical            | 2            |               |                   |
| Child                            | 6            | 2             |                   |
| Unrelated-matched               | 21           | 20            | 1                 |
| Unrelated-mismatched             | 1            | 1             |                   |
| Stem cell source                 |              |               |                   |
| Marrow                           | 120          | 118           | 2                 |
| PBSCs                            | 158          | 126           | 32                |
| GVHD prophylaxis                 |              |               |                   |
| ATG, steroids                    | 1            |               |                   |
| CYA                              | 7            |               |                   |
| CYA, MTX                         | 84           |               |                   |
| CYA, MMF                         | 1            | 92            | 0                 |
| Tacrolimus, MMF                  | 37           |               |                   |
| CY, tacrolimus, MMF              | 1            |               |                   |
| Tacrolimus, MMF, rapamycin       | 4            |               |                   |
| Tacrolimus, MTX                  | 11           |               |                   |
| CYA, MTX, Steroids              | 5            |               |                   |
| CYA, steroids                    | 24           |               |                   |
| CYA, trimetrexate                | 2            |               |                   |
| Monoclonal antibody              | 1            |               |                   |
| MTX, steroids                    | 1            |               |                   |
| MTX                              | 7            |               |                   |
Table 3. Causes of death

| Cause                        | Ablative | Nonmyeloablative |
|------------------------------|----------|------------------|
| ARDS-Idiopathic pneumonia, DAD | 8        | 1                |
| Fungus                       |          |                  |
| Aspergillus                  | 14       | 1                |
| Candida                      | 3        |                  |
| Mucormycosis                 | 1        |                  |
| Rhizopus                     | 1        |                  |
| Torulopsis                   | 1        |                  |
| Zygomyces                    | 1        |                  |
| Graft failure                | 3        | 2                |
| Acute GVHD                   | 18       | 1                |
| Chronic GVHD                 | 2        | 12               |
| Hemorrhage                   | 2        |                  |
| Multi-organ failure/VOD      | 16       | 1                |
| Pneumocystis                 | 1        |                  |
| Renal failure                | 2        |                  |
| Sepsis                       | 5        | 5                |
| E coli                       | 1        |                  |
| MRSA                         |          | 1                |
| Pneumococcus                 | 1        |                  |
| Pseudomonas                  | 1        |                  |
| Unknown                      | 4        | 2                |
| Stroke                       |          | 1                |
| Virus                        | 13       |                  |
| Adenovirus                   | 1        |                  |
| CMV                          | 5        |                  |
| Hepatitis B                  | 1        |                  |
| Herpes simplex/zoster        | 2        |                  |
| Parainfluenza                | 1        |                  |
| Respiratory syncitial        | 3        |                  |
| Esophageal cancer            | 1        |                  |
| Lung cancer                  |          | 1                |
| Progressive myeloma          | 39       | 50               |
| Pancreatitis                 | 1        |                  |
| Polyneuropathy               | 1        |                  |
| Head trauma                  | 1        |                  |

Bold numerals refer to number of patients for each heading.

Figure 1. Probabilities of OS and PFS for patients undergoing myeloablative or non-myeloablative allogeneic hematopoietic cell transplants. First line: OS of 134 patients undergoing nonmyeloablative allografting; Second line: PFS of 134 patients undergoing non-myeloablative allografting; Third line: OS of 144 patients undergoing myeloablative allografting; Fourth line: PFS of 144 patients undergoing myeloablative allografting.

Figure 2. Probabilities of OS and PFS of 88 patients undergoing tandem autologous, non-myeloablative allografting as part of front-line therapy. First line: OS; Second line: PFS.

Table 4. Hazard ratios for outcomes in patients with multiple myeloma receiving transplants from allogeneic donors, comparing patients receiving non-myeloablative conditioning to those receiving myeloablative conditioning

| Cause                  | HR (95% CI) | P      |
|------------------------|-------------|--------|
| Overall mortality      | 0.40 (0.3–0.6) | <0.0001 |
| PFS                    | 0.55 (0.4–0.8) | 0.0002 |
| TRM                    | 0.22 (0.1–0.4) | <0.0001 |
| Relapse/prog            | 1.20 (0.8–1.9) | 0.43   |
| Acute GVHD              | 0.41 (0.3–0.6) | <0.0001 |
| Chronic GVHD            | 0.86 (0.5–1.4) | 0.51   |

In order to discern any association between chronic GVHD and disease progression, we examined this association and its effects on PFS, in a time-dependent fashion among recipients of non-ablative transplants. We found only a weak association between patients with clinical extensive chronic GVHD and reduced rates of progression or relapse HR = 0.74 (0.4–1.3), P = 0.32. This resulted in no net benefit on PFS HR = 0.89 (0.5–1.5), P = 0.65.

DISCUSSION

In this retrospective review of allo-SCT for MM going back 34 years, significant improvements were observed in the TRM associated with the introduction of non-myeloablative conditioning. Mortality censored for relapse was 55% among the 144 patients receiving ablative transplants compared with only 18% in the non-myeloablative group. As a result, the survival at 10 years from transplant was significantly superior for non-ablative transplants, 35% compared with 15%. As these two groups were not prospectively studied and were not treated contemporaneously, it is likely that other factors including better anti-infectious prophylaxis and treatment, and the use of PBSCs may have contributed to the observed differences.
have contributed in part to these improvements. Indeed, there were almost no deaths due to viral or fungal pathogens among non-myeloablative recipients; a major cause of mortality among ablative transplant recipients. In addition, there were major differences between the groups in patient age, relapse after prior autologous transplant, and proportion of patients resistant to their last chemotherapy regimen just before transplant. Although the perception is that patients with MM tolerate allografting more poorly than patients with other hematologic malignancies, a recent analysis from the European Group for Blood and Marrow Transplantation suggested that when adjusted for risk factors including age, disease stage, interval from diagnosis to transplant and donor factors, outcomes for patients with MM were similar. Additionally, there are now newer drugs available to treat relapse that were not available previously which would certainly affect survival after relapsed disease.

In univariate analysis, non-myeloablative transplants were associated with an apparent greater risk of disease progression or relapse, 55% at 6 years for non-myeloablative compared with 34% for ablative conditioning. When adjusted for competing risks of death due to higher TRM associated with ablative transplants, however, these differences were not statistically significant. Although this result does not appear to agree with the analysis of others such as the EBMT registry data, the study was only a univariate analysis and did not account for competing causes of death, as ours did. Nevertheless, the amount of residual disease present at transplant, provides a greater challenge for clearance by the allogeneic donor graft when a non-myeloablative regimen is utilized and is still the primary cause of treatment failure. When comparing the incidences of chronic GVHD, 27% of the ablative recipients developed CGVHD compared with 66% for non-ablative recipients. As the risk of CGVHD is time-dependent, and more non-myeloablative patients survived the early phases of transplant, this did not prove to be significantly higher when adjusted for competing causes of death.

In an attempt to overcome this limitation, many groups have employed a tandem autologous, non-myeloablative allogeneic transplant with the aim of providing major cytoreduction, but an opportunity for the patient to recover from high-dose chemotherapy before the allo-SCT. In multivariable analysis, patients receiving a tandem autologous, non-myeloablative allogeneic transplant had reduced non-relapse mortality, but did not independently affect other outcomes. This analysis also indicated that relapse after a prior autologous transplant is associated with inferior survival as well as other outcome measures. As seen in prior studies, a t(1;2) microglobulin >4 was also independently associated with increased risk of progression or relapse as well as inferior survival. Female donors were associated with a significantly reduced risk of relapse or progression, consistent with other analyses that have shown more of a graft-vs disease effect from female to male transplants.

These analyses agree with other studies showing prior autograft failure to be one of the major risk factors for disease progression after non-myeloablative allo-SCT. The observation that prior autograft failures do poorly with an allo-SCT argues against the recommendation some have made to delay an allo-SCT until disease progression after initial treatment or autologous transplant. In some retrospective analyses, a non-myeloablative allograft was able to overcome certain high-risk FISH characteristics such as the 4;14 translocation. Our patient population contained too few patients with 4;14 to analyze this separately, however, in the multivariable analysis only high B2 microglobulin and not adverse cytogenetics were associated with inferior outcomes. This does not mean that cytogenetics are not important but merely reflect a limited number of observations in our database to directly address that question.

It is clear that reduced intensity allo-SCT regimens can result in reliable donor engraftment with a relatively low mortality compared with high-dose regimens. The immunologic effect of the allograft is, however, relatively modest requiring a prior autologous transplant for cytoreduction. Even with the tandem auto-non-myeloablative allo-SCT approach, relapses beyond 3-5 year continue to occur, making disease recurrence the primary cause of treatment failure after tandem auto, non-myeloablative allo-SCT.

Future studies of allo-SCT in MM should focus on regimens that are less toxic but able to preserve anti-tumor effects such as radioisotopes linked to antibodies that target myeloma cells or other marrow-based cells. It should be relatively easy to combine targeted radiotherapy with a non-myeloablative regimen to create a more tolerable cytoreductive protocol. It is also worth reconsidering more myeloablative regimens, as supportive care has improved greatly in the past 20 years. As previously noted, when younger patients are transplanted earlier from initial diagnosis, TRM is reduced.

Another strategy to make non-myeloablative regimens more effective would be to combine the donor graft with infusions of allogeneic donor lymphocytes or subsets of lymphocytes in the form of 'engineered grafts', for example CD4 lymphocytes, which may have a graft vs myeloma effect without increasing GVHD. It may also be possible to exploit killer-Ig-like mismatching between donor and recipient, which has been shown to result in improved PFS due to a reduced rate of relapse. Maintenance strategies, which have been shown to delay disease progression after auto-SCT may also be effective after allo-SCT. Finally, it may be worthwhile to exploit monoclonal antibodies targeting myeloma cells such as the CD40 Ag or CS-1 Ag, in order to increase the ability of donor allogeneic cells to eliminate residual host disease. In any case, due to the substantial morbidity and mortality associated with allografting as well as the uncertain benefits, future approaches to allografting for myeloma should only be performed within well-designed clinical trials.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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**Table 5. Multivariable analysis of outcomes among patients with multiple myeloma receiving transplants from allogeneic donors following non-myeloablative conditioning**

| Variable                  | Relapsed auto | Risk group* | B2M > 4.0 | Tandem auto | Female donor | No. before regimens |
|---------------------------|---------------|-------------|-----------|-------------|--------------|---------------------|
| Survival                  | 2.51 (1.1 - 5.8) | 0.03 | HR (95% CI) | P | 2.56 (1.2 - 5.6) | 0.02 | HR (95% CI) | P | 2.39 (1.1 - 5.1) | 0.03 | HR (95% CI) | P |
| PFS                       | 2.89 (1.4 - 6.1) | 0.005 | 2.45 (1.5 - 3.9) | 0.0002 | 0.16 (0.0 - 0.6) | 0.004 | NS |
| TRM                       | NS | NS | NS | NS | NS | NS |
| Rel/Prog                  | 5.42 (2.2 - 14) | 0.0003 | 3.18 (1.8 - 5.6) | <0.0001 | NS | NS | NS | 0.50 (0.3 - 0.9) | 0.01 | 0.77 (0.6 - 1.0) | 0.04 |

*aChemotherapy-responsive or -resistant disease.*
