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CD34-selected allogeneic hematopoietic stem cell transplantation for patients with relapsed, high-risk multiple myeloma

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Abstract

We report results of a retrospective analysis of 44 patients with relapsed and high-risk multiple myeloma (MM) undergoing allogeneic CD34-selected hematopoietic stem-cell transplantation (CD34-selected HSCT) from human leukocyte antigen (HLA)-compatible donors. Patients had multiply relapsed disease including relapse at <15 months after autologous transplant and most

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Authorship Statement

ES provided clinical care of patients, analyzed data and contributed to the manuscript. SD performed biostatistical analyses and contributed to the manuscript. EO collected and analyzed data. HL, AL, DC, HH, NL, OL, SG, AC and SJ provided clinical care of patients and reviewed the manuscript. GK performed the study, provided clinical care, supervised data collection and analyses, and wrote the manuscript.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

patients (28/44; 65%) also had high-risk cytogenetics. Before transplant, patients received busulfan (0.8 mg/kg X 10 doses), melphalan (70 mg/m^2 X 2 days), fludarabine (25 mg/m^2 X 5 days), and rabbit anti-thymocyte globulin (2.5 mg/kg X 2 days). Patients with 10/10 HLA-matched donors were treated prophylactically with low doses of donor lymphocyte infusions (0.5 to 1 X 10^6 CD3+/kg) starting at 4–6 months post CD34-selected HSCT. Acute (grade II–IV) graph-versus-host disease (GVHD) and transplant-related mortality at 12 months were 2% and 18%, respectively. Chronic GVHD was not observed in any patient. Overall and progression-free survival at 2 years was 54% and 31%, respectively. By multivariate analyses, the outcomes of CD34-selected HSCT were influenced by presence of extramedullary disease, disease status prior to CD34-selected HSCT and age.

This study demonstrates notable safety and efficacy of CD34-selected HSCT in patients with multiply relapsed MM including those with high-risk cytogenetics.

Introduction

Multiple myeloma (MM) is a malignant disease of plasma cells, with an estimated 25,000 new MM diagnoses annually, and about 11,000 projected patients to die of the disease every year.[1,2,3] Approximately 25% of MM patients are considered “high-risk” as defined by routine cytogenetics. Despite the introduction of immunomodulatory agents and proteasome inhibitors patients with high-risk myeloma continue to do poorly, even with tandem autologous stem cell transplantation with a median survival of approximately 3 years.[3,4]

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potential curative treatment available for patients with multiple myeloma. Despite the potential advantages of graft-versus-tumor immune responses and a tumor-free source of stem cells, the success rate of patients undergoing conventional high-dose conditioning with allogeneic bone marrow or peripheral blood stem-cell transplantation has been historically compromised by high incidences of acute and/or chronic graft-versus-host disease (GVHD) and transplant-related mortalities (TRM) exceeding 40% at day 100 post-transplant.[5–7] The introduction of non-myeloablative conditioning regimens in the treatment of myeloma has reduced associated toxicities and TRM, but high rates of acute and chronic GVHD persist.[8–10] In addition, results from transplants with non-myeloablative regimens have been poor in patients with multiply relapsed disease.[11,12] CD34+ selection has been effectively used in other hematologic malignancies as a strategy that allows intensification of the conditioning regimen while at the same time reducing the risks of acute and chronic GVHD. We have extensively studied CD34 selection in a variety of hematologic malignancy and have shown in retrospective analysis that long-term results of disease free survival and overall survival are comparable to unmanipulated grafts with significantly lower rates of acute and chronic GVHD. [13,14] Since 2007, we began performing CD34 selected allogeneic HCT in patients with relapsed MM. To determine the long-term disease specific outcomes as well as determinants of prognosis we performed a retrospective analysis of transplant outcomes on the initial 44 patients treated that are summarized herein.

Patients and Methods

Patients

We assessed the safety, toxicity, and efficacy of allogeneic CD34-selected HSCT in patients with high-risk, multiply relapsed MM at Memorial Sloan Kettering Cancer Center (MSKCC). The study was approved by the Institutional Review/Privacy Board at MSKCC and by the Food and Drug Administration.

Patients included in this study had relapsed multiple myeloma following autologous stem-cell transplantation (auto-SCT). Relapse had to occur either with normal cytogenetics within 15 months following the autologous transplant or with high-risk cytogenetics. Patients had to have achieved at least a partial response (PR) following additional chemotherapy or second salvage auto-SCT. Patients with an HLA-matched related or unrelated donor (genotypically matched at all A, B, C, DRB1, and DQB1 loci, as tested by DNA analysis) and patients who had an unrelated donor with only one antigen or one allele mismatch at the HLA A, B, C, DRB1, or DQB1 loci were eligible for entry on this protocol. All patients on study with at least 1 year of follow up post-CD34-selected HSCT at the time of analysis are presented in this report; encompassing patients who underwent allogeneic HSCT between 11/28/2007 and 10/9/2013. T-cell depletion was performed by positive CD34 selection using the Isolex 300i (Nexell Therapeutics, Irvine, CA, USA) followed by rosetting with sheep erythrocytes for the initial 13 patients (2008–09) and by CD34+ enrichment by the CliniMACS CD34 Reagent System (Miltenyi Biotech, Bergisch Gladbach, Germany) in 31 patients thereafter. Patients did not receive immunosuppressive therapy after transplantation. All patients signed written informed consent for their treatment trials.

Conditioning regimen

The preparative regimen began with busulfan at 0.8 mg/kg/dose every 6 hours for 10 doses intravenously (IV) and was administered on days −9 to −7. Busulfan doses were adjusted based on the pharmacokinetics of the first dose. Melphalan 70 mg/m^2/day IV was given on days −7 to −6, and fludarabine 25 mg/m^2/day IV was administered on days −6 to −2. Busulfan and melphalan doses were adjusted if the patient was >125% of ideal body weight as calculated on an adjusted ideal body. Rabbit anti-thymocyte globulin (ATG) was administered at 2.5 mg/kg/day on days −3 and −2. Methylprednisolone was given at 2 mg/kg/day for 2 days with the ATG administration and was discontinued thereafter.

Donor lymphocyte infusions

Recipients of 10/10 HLA-matched allografts were treated prophylactically with 5 X 10^5 CD3$^+$/kg from matched donors at 4–6 months post-transplant. A second infusion of 5 X 10^5 CD3$^+$/kg was administered 3–4 months following the first infusion. A third dose of 1 X 10^6 CD3$^+$/kg was administered 2–4 months following the second infusion. Recipients of HLA-mismatched allografts were only treated preemptively with 1 X 10^5 CD3$^+$/kg at diagnosis of relapse or progression, but no sooner than 4–6 months post-transplant. A second infusion of 5 X 10^5 D3$^+$/kg was administered 1–3 months following the first infusion. A third infusion of 1 X 10^6 CD3$^+$/kg could be administered 3–4 months following the second infusion. All patients were eligible for second and third doses of DLI only in the absence of GVHD.

Response criteria

Responses to CD34-selected HSCT and DLI were assessed 3 monthly intervals according to the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma.[15] Patients were deemed to have progressed if they had an increase from their lowest response value by >25% of any of the following 1) M-spike (absolute increase must be >0.5g/dL); 2) in patients who do not produce a measurable M-spike, the difference in the involved-uninvolved free light chains (absolute increase must be >10mg/dL); 3) BM involvement by MM cells; or 4) the development of new, or increase in size of old, bone lesions or soft tissue plasmacytomas.

Cytogenetics and FISH analyses

Bone-marrow samples were collected before HSCT and at 30 days, 100 days, 6 months, 12 months, and 24 months post-HSCT. Analysis by MSKCC clinical laboratories was performed for immunohistochemistry of CD138 and light chains. Cytogenetics and fluorescence in situ hybridization (FISH) were performed on magnetic-bead–selected CD138 positive cells isolated from bone-marrow aspirates. For the purpose of this study, patients were considered to have high-risk cytogenetics if they had at least one of the following: gain 1q, deletion 17p, complex cytogenetics, t(4;14), or t(14;16) by FISH analyses or deletion 13 by karyotyping.

Biostatistics

Overall survival (OS) and progression-free survival (PFS) from the time of HSCT were evaluated using Kaplan-Meier methodology. The logrank test and Cox proportional hazard regression were used to compare the effect of disease and transplant characteristics on the time-to-event endpoints. Cumulative incidence functions were used to estimate the incidences of grade II–IV acute GVHD and non-relapse mortality (NRM). Competing risks for NRM were relapse, and for acute GVHD were relapse and death in the absence of GVHD. All analyses were conducted using the R statistical package. [16]

Results

Patient characteristics

The pre-transplant characteristics of these patients, cytogenetics, and lines of treatment are detailed in Table I. Median follow-up among survivors was 24.8 months (range, 11.2–81.2 months). The median age at the time of the study transplant was 55.5 years (range, 32–68 years). All patients had prior auto-SCT followed by a relapse within 15 months. Eighteen of the 44 patients (40%) had two prior auto-SCTs. Additionally, 29/44 patients (65%) had high-risk cytogenetics and 13/44 patients (29%) were diagnosed with extramedullary disease manifestations prior to CD34-selected HSCT. All patients had 3–10 prior lines of treatment; 16 patients (36%) had >6 prior lines of treatment, 16 (36%) had 5–6 prior lines, and 12 (27%) had 3–4 lines. Median time from diagnosis to CD34-selected HSCT was 41 months. For 32 patients (72%), 10/10 HLA-matched donors were available (14 sibling donors; 18 matched unrelated donors), while the remaining 12 patients (28%) had 9/10 HLA-mismatched unrelated donors.

Graft composition and engraftment

T-cell depletion performed by both methods achieved a median of 2.4 X 10^3 CD3+/kg (range, 4.72 X 10^2 to 1.29 X 10^4 CD3+/kg) for all patients. See Table II for complete graft composition of all 44 patients. No significant differences in the graft composition were observed when T-cell depletion was performed for the initial 13 patients by positive CD34 selection followed by rosetting with sheep erythrocytes compared to the subsequent CD34+ enrichment in the other patients (data not shown). All patients engrafted promptly at a median of 10 days post CD34-selected HSCT (range, 9–12 days). None of the patients developed graft failure or graft rejection.

Overall survival and progression-free survival

The clinical outcomes of all 44 patients are shown in Figure 1. The median PFS of 13.5 months translates into a PFS for all patients of 31% (95% CI: 0.19, 0.5) at 2 years and 18% (95% CI: 0.09, 0.40) at 4 years with an OS of 54% (95% Confidence Interval [CI] 0.41, 0.72) at 2 years and 42% (95% CI: 0.28, 0.63) at 4 years. There was no difference in outcome based on transplants from related (n = 14) vs unrelated (n = 30) donors or unrelated 10/10 matched (n = 18) vs 9/10 matched (n = 12) donors (Table III).

When we analyzed the OS and PFS based on the number of lines of therapy administered prior to CD34-selected HSCT, we found a trend towards better OS and PFS in patients with ≤6 lines of treatment compared to those with >6 lines of treatment. For these analyses, auto-SCT followed by maintenance therapy and tandem auto-SCT plus maintenance therapy were considered a single line of treatment (Figure 2). OS at 2 years for patients with 3–4 lines, 5–6 lines, and >6 lines of treatment were 67% (95% CI: 0.45, 0.99), 60% (95% CI: 0.39, 0.91), and 33% (95% CI: 0.14, 0.76), respectively. PFS at 2 years for patients with 3–4, 5–6, and >6 lines of treatment were 42% (95% CI: 0.21, 0.81), 41% (95% CI: 0.22, 0.76), and 0%, respectively. As demonstrated in Figure 3A, there is a significant difference ($P = 0.03$) in OS based on disease status prior to CD34-selected HSCT. Patients achieving a very good partial response or a complete response (VGPR/CR; n = 23) demonstrated 2-year OS estimates of 62% (95% CI: 0.44, 0.87) and while those with only a PR (n = 21) had 2-year OS estimates of 47% (95% CI: 0.29, 0.74). There was a trend but no significant difference in PFS ($P = 0.12$) in these two subgroups (Figure 3B), with 40% (95% CI: 0.24, 0.68) and 14% (95% CI: 0.03, 0.70), respectively. We also performed CD34-selected HSCT for 13 patients with relapsed MM and high-risk cytogenetics who were diagnosed with extramedullary manifestation of disease prior to allotransplant. Patients with extramedullary disease had significantly poorer OS and PFS when compared to those without extramedullary disease. As shown in Figure 4, the OS and PFS at 2 years for patients with extramedullary disease was only 31% (95% CI: 0.14, 0.7) and 8% (95% CI: 0.01, 0.51), compared to 66% (95% CI: 0.51, 0.86) and 41% (95% CI: 0.26, 0.67), respectively, for patients without extramedullary manifestation. The OS and PFS results including 95% Confidence Intervals for all patient cohort analyses at 2 and 4 years post CD34-selected HSCT are summarized in Table III. Overall, the two-year cumulative incidence of relapse was 51% (95% CI: 0.34–0.66) in our patient population.

Based on the univariate results above and listed in Table III, a multivariable model for OS was constructed. The three factors remained significant in the multivariable model; the model included extramedullary manifestation (HR: 3.18 (95% CI: 1.34–7.58); p-value 0.009), pre-transplant disease status (less than VGPR, HR: 3.80 (95% CI: 1.56–9.18); p-value: 0.003) and age (HR: 3.96 (95% CI: 1.44–10.83); p-value: 0.007). Among the 13 patients with extramedullary disease only 4 patients had > 6 lines of treatment prior to CD34-selected HSCT. We were also interested in analyzing the effect of the conditioning regimen of busulfan/melphalan/fludarabine (Bu/Mel/Flu) on patients who did not achieve a CR prior to CD34-selected HSCT. After salvage treatment, at the time of conditioning chemotherapy 21/44 (48%) patients were in CR or VGPR. The remaining 52% of patients had overt residual disease at the time of transplant. Using the post-salvage treatment outcome as a new baseline to assess their response to Bu/Mel/Flu conditioning chemotherapy, we demonstrated that this regimen had potent additional anti-myeloma activity. At 100 days post CD34-selected HSCT evaluation, there was an overall response rate (CR+PR) of 70%, including the induction of CRs in 39%, in this relatively refractory, multiply relapsed patient population that had suboptimal responses to salvage therapy. Overall, the Bu/Mel/Flu conditioning was very well tolerated as evidenced by only 1/44 (2%) patient death by 100 days post-transplant, low overall TRM, and the rapid engraftment in these patients after CD34-selected HSCT.

Graft-versus-host disease and non-relapse mortality

Standard Blood and Marrow Transplant Clinical Trials Network and International Bone Marrow Transplant Registry systems clinical criteria as defined by Rowlings et al[17] were used to establish and grade acute GVHD.

The event of grade II–IV acute GVHD was seen at a low rate (2%; 95% CI: 0.002, 0.11) (Figure 5A). Only one patient developed acute GVHD of the lower GI tract and died of complications thereof. There was no observed GVHD after DLI infusions. No patients were diagnosed with chronic GVHD.

As shown in Figure 5B, the non-relapse mortality at one year was overall 18% (8/44 patients; 95% CI: 0.08, 0.31). Of these patients, 2 experienced nosocomial infections of oseltamivir-resistant influenza A during the neutropenic period and subsequently succumbed. One patient developed de novo acute toxoplasmosis following a business trip (against medical advice) only 3 months after transplant. Both patient and donor were seronegative for toxoplasmosis prior to transplant. Two patients developed antiviral drug-resistant cytomegalovirus disease and 2 patients died of gram-negative sepsis. The NRM was higher ($P = 0.05$) in patients who only achieved a PR (29%; 95% CI: 0.11, 0.49) compared to the patients in VGPR/CR (9%; 95% CI: 0.01, 0.25) prior to CD34-selected HSCT (Figure 5C).

Donor lymphocyte infusions

In order to boost the graft-versus-malignancy effect, for patients with 10/10 HLA-matched donors administration of 2–3 doses of DLI were planned prophylactically beginning at 4–6 months post-transplant. 19/31 patients with 10/10 matched donors received DLI, reasons to

have not received DLI include illness or death (n=11) at the time of eligibility or GvHD (n=1). 5/13 patients with mismatched donors went on to receive DLI at the time of progression. Mismatched patients did not receive DLI because they are either still in remission (n=3), or illness or death (n=5). Six patients were in CR at the time of initial DLI. These patients outperformed the group as a whole with all 6 in CR at 1-year post-transplant and survival data as follows: 15.4 months, 60.2 months, and 4 patients still alive with OS ranging between 22–57 months (data not shown). A first dose of DLI was given to 18 patients with residual disease either because they did not reach CR from salvage and transplant conditioning or because they were given this dose at the time of progression. Of the 18 patients who received their initial dose of DLI with residual disease, 4 (22%) were restored to CR and were in CR at 1 year post-completion of an initial doses of DLI. Importantly, none of our patients developed GVHD as result of DLI at the doses administered.

Discussion

We demonstrate that CD34-selected HSCT has remarkable safety and improved efficacy when compared to historic controls of allogeneic transplants for MM and provides a platform to integrate post-transplant immunotherapeutic approaches to improve outcome.

Multiple previous studies have demonstrated a median PFS of only 7–8 months in patients with high-risk cytogenetics after high-dose therapy and autologous stem-cell transplantation.[3,4] Outcome is even worse if patients relapse post-auto-SCT with high-risk cytogenetics or within a short time period.[10,11] Risk-adapted strategies for these high-risk patients are warranted, such as consideration of allogeneic SCT, which provides a potential for prolonged remission or even cure. However, myeloablative allogeneic transplants for MM historically have been plagued with unacceptably high rates of GVHD and TRM.[19] As a consequence, many institutions have shifted to providing non-myeloablative transplants for MM, which has reduced the TRM 8% to 16% in reported large institutional studies, but rates of GVHD remain unacceptably high. These studies report grade II–IV acute GVHD of 17% to 43% and chronic GVHD of 54% to 63%, with up to 32% of patients with extensive GVHD despite the long-term immunosuppressive therapy that is required following non-myeloablative transplants.[8,9,20–22]

In response to these restrictions and limited clinical options for patients with high-risk MM who may otherwise benefit from allogeneic transplant, we investigated myeloablative CD34-selected HSCT as a potentially safer alternative. Our results demonstrate only 2% acute GVHD (Figure 5A) and no chronic GVHD in our patient cohort, despite having 61% (27/44) of transplants coming from unrelated donors, nearly half of which (13/27; 48%) had a mismatched antigen/allele. The administration of DLI post-transplantation at calculated doses given on our study was not associated with GVHD.

Overall, our myeloablative conditioning regimen with Bu/Mel/Flu was very well tolerated with median engraftment on day 10 post-transplant. Although still favorable with 18% at one year (Figure 5B) and comparable to the NRM obtained after non-myeloablative transplants,[9, 10, 18–20] the NRM in this study is higher compared to NRM obtained in other

clinical trials with this chemotherapy regimen obtained at our center.[23] This may be explained by the nosocomial infections of 2 patients with oseltamivir-resistant influenza on this study and one patient who developed de novo toxoplasmosis infection. Overall causes of NRM were infection (n=7) and GvHD (n=1). In addition, the NRM was particularly poor in patients who only achieved a PR compared to patients who were in VGPR or CR (29% vs 9%; P =0.05) (Figure 5C).

Overall, our median PFS of 13.5 months, which translates into PFS of 55% at one year and 31% at two years, compares very favorably to other reported studies, especially since all of our patients were heavily pretreated with multiple lines of chemotherapy and all relapsed after autologous transplant. In fact, 18/44 patients (40%) underwent two autologous transplants, of which 13/18 patients (72%) required a salvage auto-SCT to obtain at least a partial remission in order to proceed to CD34-selected HSCT (Table I). Our study also included a cohort of 13 patients who presented with extramedullary disease prior to CD34-selected HSCT. As shown in Figure 4, these patients had a particularly poor OS and PFS at 2 years of 31% and 8%, respectively. If patients with extramedullary disease were excluded from these analyses (n = 31), we achieved an OS and PFS of 66% and 41%, respectively, at 2 years and OS 53% and PFS 30% at 4 years (Table III).

The large institutional studies for patients with MM undergoing non-myeloablative transplants reported PFS ranging from 36% to 58% at 3 years.[9, 10, 18–20] In contrast to our patient cohort, those patients underwent transplant exclusively from their sibling donors following an auto-SCT, and the majority of these patients had normal cytogenetics. In fact, transplants with non-myeloablative regimens showed only a 2-year PFS and OS of 19% and 32%, respectively, if patients had failed prior autologous bone-marrow transplantations.[12] Outcome with non-myeloablative transplants was limited in all studies if patients presented with high-risk cytogenetics and/or chemo-insensitive disease.[11,13] Strikingly, the limited outcomes of these studies were accompanied by high rates of acute and chronic GVHD as detailed above. This is in contrast to the low rate of acute GVHD and absence of chronic GVHD in our study, raising the overall question: Is chronic GVHD beneficial at all in patients undergoing allotransplant for MM? In fact, a recent publication from the European Society for Blood and Marrow Transplantation registry describes the lack of benefit of GVHD in a variety of diseases and particularly in patients with plasma-cell disorders,[24] supporting the promising outcome in particular subsets of patients in the absence of GVHD in our study.

While overall our OS and PFS compare favorably to historical results, there is still room for improvement of the relapse rate, particularly for patients who have failed >6 lines of prior therapy or have extramedullary involvement. Given the safety of CD34-selected allogeneic transplant presented here, we may consider an earlier allogeneic transplant performed for patients with high-risk MM before multiple lines of chemotherapy have been administered and clinical responses are limited to partial remissions with remaining treatment options.

Recently, improvement in inducing complete remissions and PFS in patients with relapsed myeloma following 1–3 prior treatments with carfilzomib, lenalidomide, and dexamethasone has been reported.[25] This combination provides a potentially new induction regimen that

could be considered in multiply relapsed patients prior to CD34-selected HSCT. In young patients with relapsed high-risk disease, this regimen may also provide the clinical responses needed to improve the outcome following consolidative CD34-selected HSCT and provide long-term PFS.

The existence of a GVM effect has been directly confirmed by the results of DLI in patients who relapsed after failure of conventional allografts.[26–29] Salama et al. reported results on 25 patients who received DLI (median dose 1 X 10^8 mononuclear cells/kg) for MM after relapsing after an allograft. Overall, 7 of 15 pts achieved a CR.[28] Lokhorst reported on 27 patients receiving DLI following partially T-cell–depleted allotransplants.[26] Overall, 14 of 27 patients responded, 5 with CRs. Responding patients received at least 1 X 10^8 mononuclear cells/kg. However, all responding patients developed GVHD following administration of the relatively high doses of donor T lymphocytes.

We administered doses of donor-derived $CD3^+$ T cells in the range of 5 X 10^5/kg to 1 X 10^6/kg $CD3^+$ from matched donors with a first dose administered 4–6 months post CD34-selected HSCT. We did not observe development of GVHD post-DLI, but found the development of donor-derived, antigen-specific T-cell responses, that correlated with clinical responses as previously described. [18] Our patients were not receiving post-transplantation immunosuppressive therapy, which likely significantly contributed to the observed outgrowth of donor-derived, antigen-specific, T-cell responses.[18]

In summary, we demonstrate that CD34-selected HSCT significantly reduces acute and chronic GVHD and associated transplant-related mortality. Given the high-risk, multiply relapsed nature of this patient population it is important to note that the reduction in toxicity does not compromise overall clinical responses when compared to historical and contemporary studies of allogeneic transplants for MM as evidenced by a “tail on the curve” that indicates durable responses in a cohort of these patients. This approach provides the safety and efficacy to consider risk stratification for younger patients with high-risk disease to undergo transplant at an earlier time before most chemo combinations have been exhausted. The lack of immunosuppressive therapy post CD34-selected HSCT provides further additional options to include post-transplant immunotherapeutic approaches to improve on disease recurrence. The presence of extramedullary disease is associated with a particularly poor outcome and the effect of immunotherapy on extramedullary sites remains to be determined.

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Highlights

- CD34-selected HSCT demonstrates notable safety in patients with multiply relapsed MM
- CD34-selected HSCT permits lasting remissions in the absence of graft-versus-host disease
- CD34-selected HSCT provides a platform for adoptive immunotherapeutic approaches

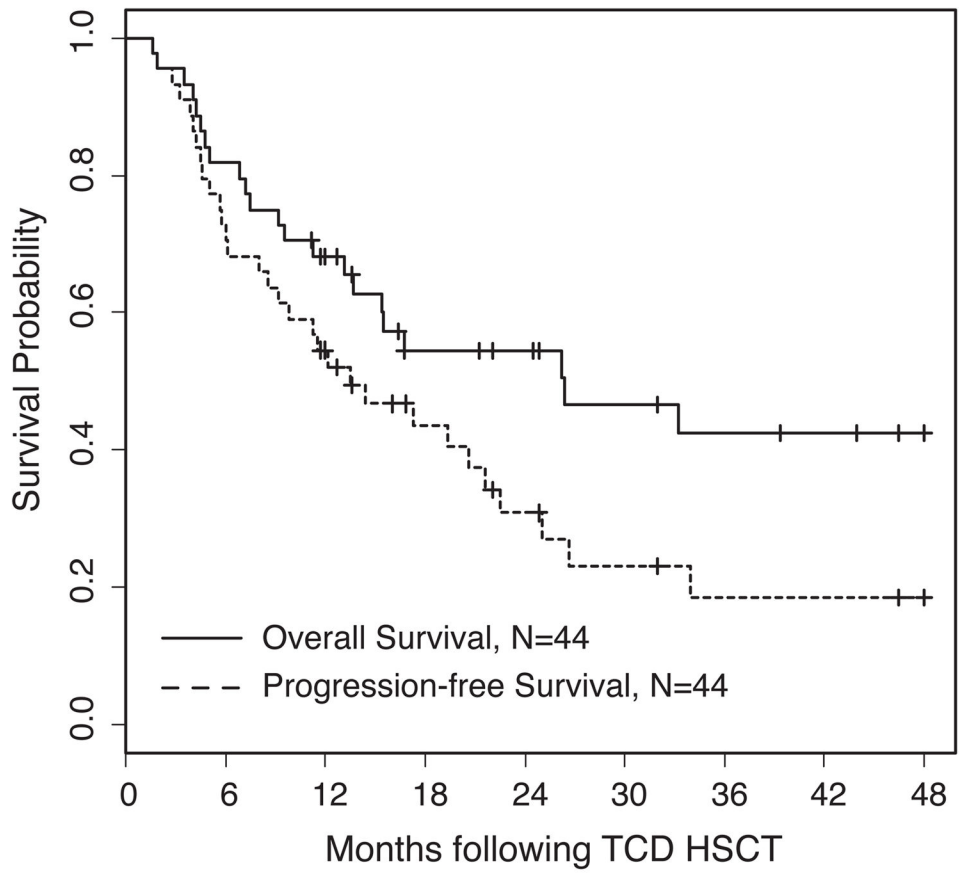

Figure 1.
Overall and progression-free survival of 44 patients with multiply relapsed multiple myeloma undergoing CD34-selected HSCT.

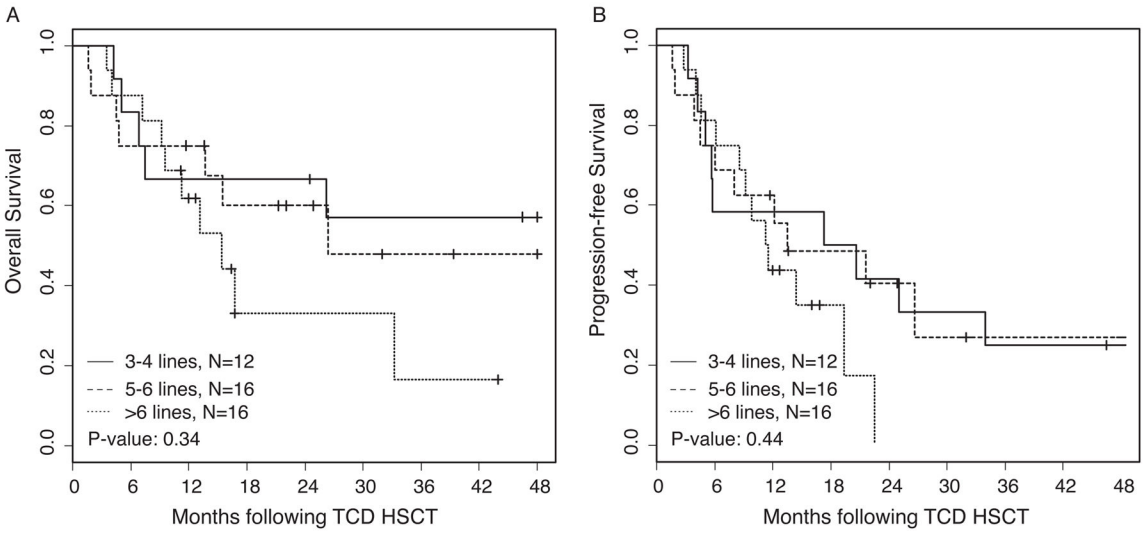

Figure 2. Overall and progression-free survival based on lines of treatment prior to CD34-selected HSCT

For these analyses, auto-SCT followed by maintenance therapy and tandem auto-SCT plus maintenance therapy were calculated as a single line of treatment as detailed in Table I.

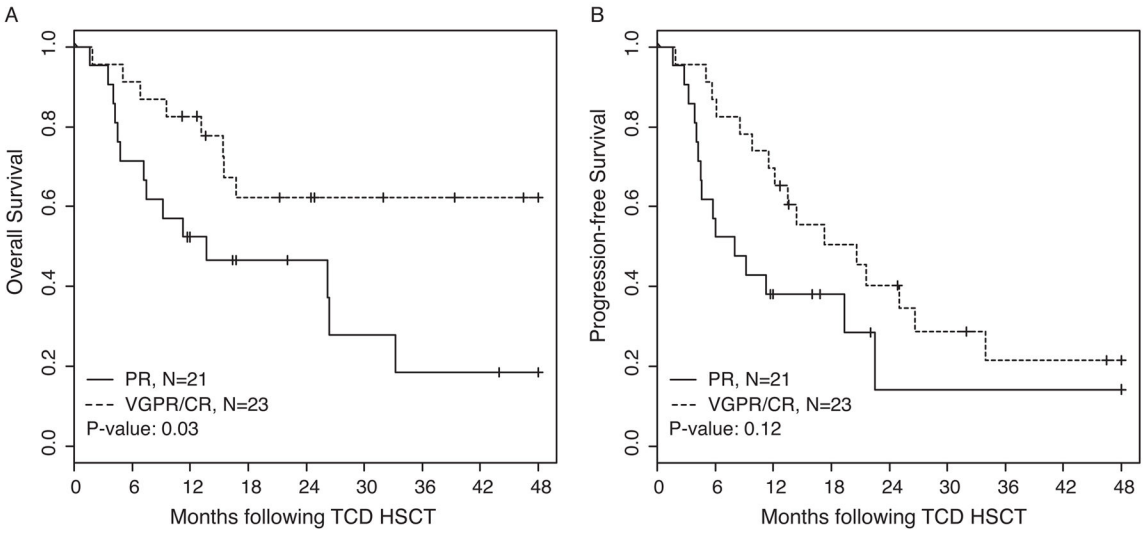

Figure 3. Overall and progression-free survival based on disease status prior to CD34-selected HSCT

Partial remission (PR) vs very good partial remission (VGPR) / complete remission (CR)

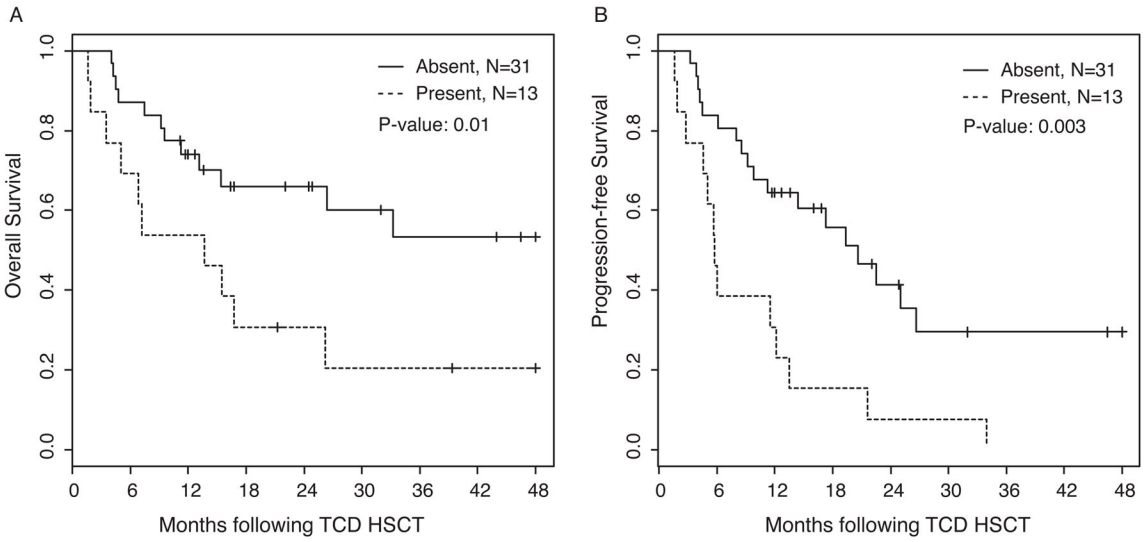

Figure 4.

Overall and progression-free survival based on presence (n = 13) or absence (n = 31) of extramedullary manifestation prior to CD34-selected HSCT.

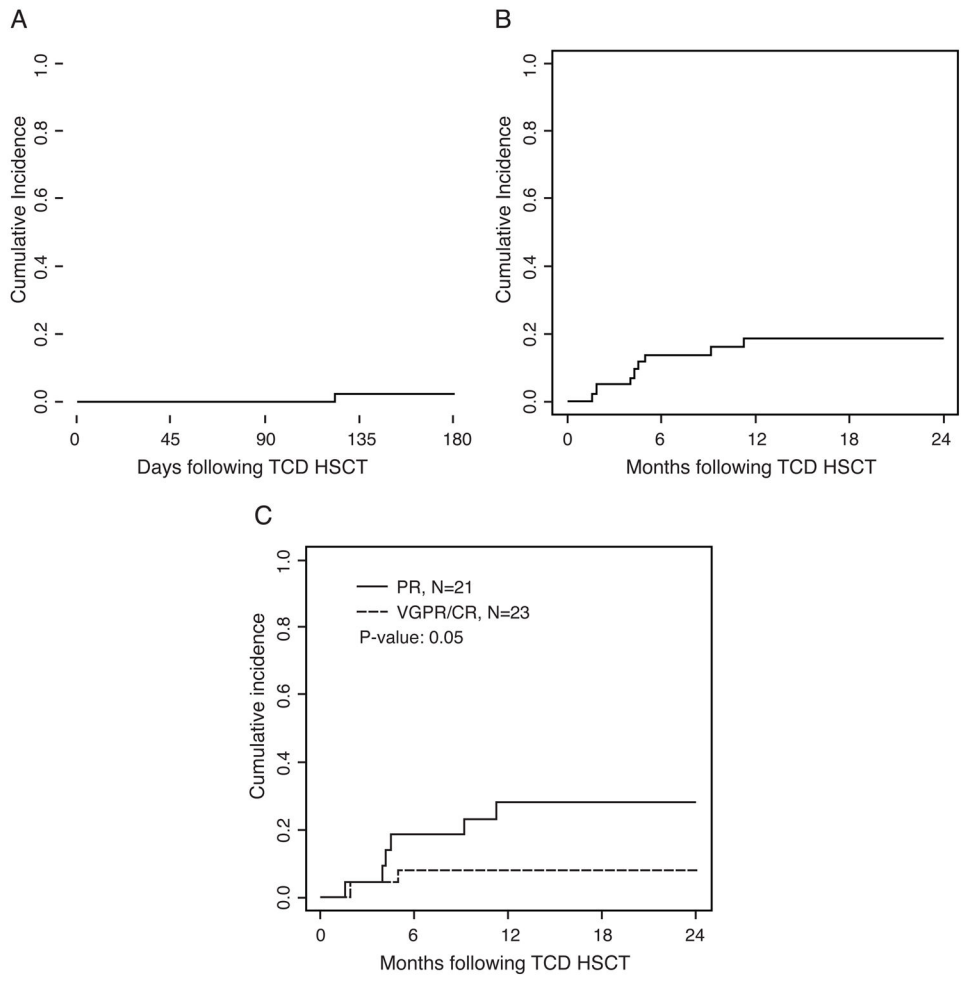

Figure 5. Acute GVHD and non-relapse mortality (NRM)

(A) Acute GVHD (grade II–IV) to days +180 post CD34-selected HSCT, (B) NRM post CD34-selected HSCT and (C), NRM based on disease status (PR; n = 21) or (VGPR/CR; n = 23) prior to CD34-selected HSCT.

Table I

UPN#	MM	Cytogenetics	Prior Lines of TX (Detail)	Pri or Lines of TX	Age at BMT	BMT	Match	Donor
1	IgG Kappa	Normal	TD, Mel + tandem auto SCT, RVD	3	42	11/28/2007	9/10	Unrelated
2	IgA Lambda	t(4;14), del 13q	BD x 6; Mel + auto SCT; RD; VD	4	38	6/18/2008	10/10	Related
3	IgG Kappa	del 13q	TD; Mel + auto SCT; VTD	3	32	8/20/2008	10/10	Related
4	IgG Lambda	del 17p, del 13q	TD; Bortez; auto SCT; VAD; VP-16/Cytoxan	5	57	3/4/2009	10/10	Unrelated
5	IgG Kappa	t(4;14)	BIRD; Cytoxan, Mel + auto SCT; RVD	3	69	4/30/2009	10/10	Related
6	IgG Kappa	t(4;14)	TD→RVD; Cytoxan→Mel + tandem auto SCT; BDD	3	54	9/3/2009	10/10	Unrelated
7	IgG Lambda	11q23, t(4;14), del 17p	VAD x 4; Mel + tandem auto SCT; RVD x 9	3	54	10/23/2009	10/10	Related
8	IgG Lambda	t(4;14), del 13q	RD; Mel + tandem auto SCT; BD, XRT; DCEP; RVD	5	49	11/20/2009	10/10	Unrelated
9	IgA Lambda	del 17p, t(4;14)	TD; BT x 3; AMD310–3102→Mel + auto SCT #1; RD→RVD; monoclonal antibody BT-062; DCEP + Thal; Mel + Bortez + auto **SCT #2**	7	48	12/17/2009	10/10	Related
10	IgG Kappa	MLL, del 13q	BDD, TD; Mel + auto SCT; CyBorD; RVD	4	57	12/24/2009	8/10	Unrelated
11	IgA Kappa	del 13q, del 14q32	TD, XRT; auto SCT #1; VTD; Mel + auto **SCT #2**	4	46	1/15/2010	10/10	Related
12	IgA Kappa	del 13q, 1q23	TD; Cytoxan→Mel + auto SCT #1; RD; BD; DT-PACE; Mel + auto **SCT #2**	6	68	1/21/2010	10/10	Related
13	IgG Kappa	t(4;14), del 13q	BDD; Mel + auto SCT; RVD	3	56	3/5/2010	10/10	Related
14	IgG Kappa	Normal	XRT, RD x 5; Auto SCT; RVD x 3; VDT-PACE x 2	4	65	8/13/2010	10/10	Related
15	IgG Kappa	Normal	BDD x 3; TD x 2; Mel + auto SCT; XRT; RD x 5; CyBorD; Mel + auto **SCT #2,** XRT	7	63	8/19/2010	9/10	Unrelated
16	IgG Kappa	Normal	BD x 2; BDD x 2; BDD/Rev x 1; Mel + tandem auto SCT, Thal maintenance; RVD x 6; DT-PACE x 2	6	58	8/25/2010	9/10	Unrelated
17	IgA Lambda	extra1q, del(13q), t(4;14)	COP + MP; Thal; Thal; BDD x 3; Mel + auto SCT #1, Thal maintenance; RD x 4; RVD; BDD x 2; VDT-PACE x 4; Mel + auto **SCT #2**	10	59	9/8/2010	9/10	Unrelated
18	IgG Kappa	del(13q), der(1)	TD→Dex x 5; Mel + tandem auto SCT, TD; XRT; Bortez + Doxil; Revlimid; BD; RD; DCEP x 7	8	61	11/10/2010	9/10	Unrelated
19	IgG Lambda	Normal	CyD x 2; BD x 2; Mel + auto SCT #1; VD; RD/Mel; Mel + auto **SCT #2**	6	57	12/2/2010	10/10	Related
20	IgG Kappa	Normal	TD x 4; RVD→RD x 5; Mel + auto SCT #1; RVD	4	54	12/10/2010	10/10	Unrelated
21	IgG Kappa	p53, tri 17, 5p, 11, 15	BiRD x 5; Mel + auto SCT #1; RVD; Rev maintenance; CyBorD x 5; VDT-PACE x 2; Mel + auto **SCT #2**	7	37	3/2/2011	10/10	Unrelated

UPN#	MM	Cytogenetics	Prior Lines of TX (Detail)	Pri or Lines of TX	Age at BMT	BMT	Match	Donor
22	IgG Kappa	Normal	BDD x 3; TD x 2; Rev; Mel + auto SCT #1, Rev maintenance; Mel + auto **SCT #2,** Rev maintenance; VDT-PACE x 2; R-VDC x 3	7	49	4/14/2011	10/10	Unrelated
23	Nonsecretory	del(20q), del(13q), del(17p), p53	pulse dose dex; VAD x 4; BD x 4; Mel + auto SCT #1, BD maintenance; RD; Mel + auto **SCT #2**; BiRD maintenance	7	63	4/20/2011	10/10	Related
24	IgG Kappa	MLL, del(13q), IgH, p53	pulse dose dex x 2; BBD x 2; TE x 2; Mel + tandem auto SCT, XRT, maintenance Thal; RVD x 10	5	45	5/26/2011	10/10	Unrelated
25	IgG Lambda	extra 1q23 and 19p13, IgH, MLL, del p53, extra of 1q, 1p, del(13) and del(17p), extra 4, 11, and 14	TD x 3; BD x 3; RD, VD-PACE x 1; VD-PACE x 3; Mel + auto SCT; Bortez mainenance	7	60	6/3/2011	10/10	Unrelated
26	IgG Lambda	extra 1q25, mono 13, Der3, 15p, 15q, trans IgH locus, del(17p)	TD x 1; RD x 4; Cytoxan→Mel + auto SCT #1; XRT/-Dex→RD x 6; Mel + auto SCT #2, Rev maintenance; CyBorD x 3; CyBorD x 2	7	62	8/31/2011	10/10	Unrelated
27	IgG Lambda	Dup(1q), del(4p), 1q25, tri(9), mono(13), tri 15, mono 16, loss p53 gene, MLL	RVD→RD x 4; Mel + auto SCT #1; RVD→RD→R; DCEP + RVD→RD; BD + Benda; VDT-PACE x 1; Mel + auto **SCT #2**	7	56	9/21/2011	9/10	Unrelated
28	IgG Kappa	del(1)(p13p22), +3, +5,+9, +11, del(13), (q12q14), del(14)(q24), der(16), t(11;16), p13.1;q24	RVD x 9; XRT; Mel + auto SCT #1; VD x 3; RVD; VDT-PACE x 3; Mel + auto **SCT #2**	7	61	10/21/2011	9/10	Unrelated
29	Lambda LC	Normal	T-BiRD; Mel + auto SCT; maintenance Rev; RD; RVD x 1→VD x 6	5	56	12/29/2011	10/10	Unrelated
30	IgG Lambda	Normal	RVD x 6; Cytoxan→Mel + auto SCT #1, maintenance Rev; ClaPD x 5; Car x 3; VDT-PACE; Mel + auto **SCT #2**	6	50	2/1/2012	10/10	Related
31	IgA Kappa	extra 1q25, trisomy 5, 9, 15; del12p1q	XRT, BD x 2, BDD x 2; Cytoxan→Mel + auto SCT, Rev maintenance; CyBorD x 4; VDT-PACE x 3	5	59	4/20/2012	9/10	Unrelated
32	Nonsecretory	mono 13, t(11;14)	TD x 3; Bortez + TD x 2; Mel + tandem auto SCT; Rev/Dex/ Lorvotuzumab/Mertansine x 9; BD x 4	5	52	8/1/2012	10/10	Unrelated
33	Kappa LC	Normal	RVD x 4; Mel + auto SCT, boost for graft failure; Rev/Bortez maintenance; Vel-CT→Vel-C x 2	4	48	9/5/2012	10/10	Unrelated
34	IgG Lambda	del 13q, del20q, extra 1q25, del4, 12, 16	RVD x 4; VDT-PACE; Mel + auto SCT #1; CyBorD x 4; Bortez/Mel + auto **SCT #2**	5	44	12/28/2012	10/10	Unrelated
35	IgG Lambda	at relapse: t(11;14), gain of chromosomes 11 and 14, del 13q	VAD + Cytoxan; BiRD; BT-D; Mel/Benda + auto SCT; DT-PACE; CRd	6	62	1/2/2013	10/10	Unrelated
36	IgA Kappa	extra copy of 1q, t(7;15), mono 7, 13, 14, 22	first pulse dose Dex; BDD; TD x 2; Mel + auto SCT #1; RVD x 4→RD→RD→TD; Mel + auto **SCT #2**; CyBorD x 4; VDT-PACE x 3	8	64	1/11/2013	9/10	Unrelated
37	IgG Lambda	t(4;14), tri 5, 9, 15 t(4;14), extra	BD x 4; Mel + auto SCT #1; Mel + auto **SCT #2**; BD x 4, VAD x 3;RD x 6, RVD, VTD; ClaPD; Cytoxan/Car	8	57	3/15/2013	1010	Related
38	IgG Kappa	of 1, extra of MLL Normal	RVD x 3.5; XRT; VDT-PACE x 2; Mel + auto SCT; BiRD maintenance; VDT-PACE x 2	6	60	4/12/2013	9/10	Unrelated

UPN#	MM	Cytogenetics	Prior Lines of TX (Detail)	Pri or Lines of TX	Age at BMT	BMT	Match	Donor
39	IgG Lambda	Normal	RD x 4; Cytoxan→Mel + auto SCT; RD; Bortez→BD; CyBorD; VDT-PACE x 2	6	55	4/18/2013	10/10	Unrelated
40	IgG Lambda	mono 13, IgH rearrangement, t(11;14), extra 1q25, del 13q14.3, 4 copies ETV6, 4 copies CBFB, 4 copies of 17	RVD; RVD + Cytoxan; Mel + VDT-PACE; Mel/VRD-PACE + Auto SCT; Mel/VDT-PACE x 2; Mel/VRD-PACE + 2nd Auto SCT; maintenance alternating VRD and VMD; VDT-PACE; VDT-PACE/Mel + auto **SCT #2**; Car/Dex	9	39	6/14/2013	10/10	Unrelated
41	IgA Kappa	loss of p53, extra MLL	RVD x 3; Mel + auto SCT #1; Bortez maintenance; Mel + auto **SCT #2**, Rev maintenance; RVD; VDT-PACE x 1	6	48	8/8/2013	10/10	Related
42	IgG Kappa	multiple copies MLL, extra copies 19p13	TD; Cytoxan; mel + auto SCT #1, Thal maintenance; RD; RVD x 4; Car/Mel + auto **SCT #2**	6	56	8/21/2013	10/10	Unrelated
43	IgG Kappa		RD x 2; RVD x 3; VDT-PACE;; Mel + tandem auto SCT; anti-PD1 antibody; Carfilzomib/Cytoxan/Dex x 6	7	53	10/3/2013	9/10	Unrelated
44	Kappa LC	del(13q), 1 copy IgH	RVD x2; VD x 1; Cytoxan; RD, RVD, RD, Rev maintenance, RD; Mel + auto SCT; Dex; CyBorD x 2; Pom/Dex x 3; Car-Pom-d; VDT-PACE	10	46	10/9/2013	9/10	Unrelated

Abbreviations

BDD = Bortezomib, Doxil, Dexamethasone
BD = Bortezomib, Dexamethasone
BiRD = Biaxin, Clarithromycin, Revlimid, Dexamethasone
BT-D = Biaxin, Thalidomide, Dexamethasone Carfilzomib,
Car-Pom-d = Pomalidomide, Dexamethasone Clarithromycin,
ClaPD = Pomalidomide, Dexamethasone
COP = Cyclophosphamide, Vincristine, Prednisone
CRd = Carfilzomib, Revlimid, Dexamethasone
CyBorD = Cyclophophamide, Bortezomib, Dexamethasone
CyD = Cyclophosphamide, Dexamethasone Dexamethasone,
DCEP = Cyclophosphamide, Etoposide, Cisplatin Revlimid,
LD = Dexamethasone
MP = Melphalan, Prednisone
RVD = Revlimid, Velcade, Dexamethasone
R-VDC = Revlimid, Velcade, Dexamethasone, Cyclophosphamide
RD = Revlimid, Dexamethasone
TD = Thaldomide, Dexamethasone
TAD = Thalidomide, Adriamycin (doxorubicin), Dexamethasone
T-BiRD = Thalidomide, Biaxin, Clarithromycin, Revlimid, Dexamethasone
VAD = Vincristine, Adriamycin, Dexamethasone
VEL-CT = Velcade, Cyclophosphamide, Thalidomide
VB = Velcade, Bendamustine
VDT-PACE = Velcade, Dexamethasone, Thalidomide, Cisplatin, Adriamycin, Cyclophosphamide, Etoposide
VTD = Velcade, Thalidomide, Dexamethasone

Table II

	Graft composition (N = 44pts)				
	CD34+/kg	**CD3+/kg**	**CD4+/kg**	**CD8+/kg**	**CD3−CD56+/kg**
Median	8.06×10^6	2.39×10^3	1.10×10^3	1.05×10^3	9.56×10^2
Range	$2.0 \times 10^6 - 1.72 \times 10^7$	$4.73 \times 10^2 - 1.29 \times 10^4$	$0 - 5.01 \times 10^3$	$0 - 3.44 \times 10^3$	$0 - 1.39 \times 10^4$

Table III

		Overall Survival				Progression-free Survival			
	N	**2-yr (95% CI)**	**4-yr (95% CI)**	**HR (95% CI)**	**P-value**	**2-yr (95% CI)**	**4-yr (95% CI)**	**HR (95% CI)**	**P-value**
Overall	44	0.54 (0.41–0.72)	0.42 (0.28–0.63)	-	-	0.31 (0.19–0.5)	0.18 (0.09–0.4)	-	-
Gender					0.91				0.46
Female	13	0.57 (0.34–0.95)	0.43 (0.2–0.92)	(reference)		0.51 (0.29–0.9)	-	(reference)	
Male	31	0.53 (0.38–0.75)	0.42 (0.26–0.68)	1.05 (0.43–2.57)		0.24 (0.12–0.47)	0.19 (0.08–0.43)	1.35 (0.6–3.03)	
Age					0.007				0.02
Less than 55	20	0.79 (0.62–1)	0.7 (0.5–0.98)	(reference)		0.46 (0.26–0.79)	0.27 (0.11–0.68)	(reference)	
55 or older	24	0.35 (0.19–0.62)	0.21 (0.08–0.52)	3.72 (1.43–9.65)		0.2 (0.09–0.45)	0.13 (0.04–0.42)	2.46 (1.17–5.14)	
Prior Lines of Therapy					0.34				0.44
3–4 lines	12	0.67 (0.45–0.99)	0.57 (0.35–0.94)	(reference)		0.42 (0.21–0.81)	0.25 (0.09–0.67)	(reference)	
5–6 lines	16	0.60 (0.39–0.91)	0.48 (0.26–0.88)	1.17 (0.38–3.57)		0.41 (0.22–0.76)	0.27 (0.1–0.75)	0.99 (0.40–2.41)	
> 6 lines	16	0.33 (0.14–0.76)	-	2.04 (0.70–5.95)		0	0	1.64 (0.65–4.12)	
Donor					0.68				0.55
Related	14	0.56 (0.35–0.9)	0.38 (0.18–0.78)	(reference)		0.30 (0.12–0.73)	0.1 (0.02–0.62)	(reference)	
Unrelated	30	0.53 (0.37–0.76)	0.47 (0.3–0.73)	0.84 (0.36–1.95)		0.32 (0.18–0.56)	0.25 (0.12–0.52)	0.80 (0.39–1.65)	
Match					0.65				0.33
10/10 Unrelated	18	0.57 (0.36–0.9)	0.57 (0.36–0.9)	(reference)		0.36 (0.18–0.72)	0.36 (0.18–0.72)	(reference)	
9/10 Unrelated	12	0.44 (0.22–0.89)	0.29 (0.1–0.85)	1.29 (0.43–3.89)		0.25 (0.08–0.73)	0.12 (0.02–0.72)	1.60 (0.63–4.08)	
Extramedullary Manifestation					0.01				0.003
Absent	31	0.66 (0.51–0.86)	0.53 (0.36–0.79)	(reference)		0.41 (0.26–0.67)	0.30 (0.15–0.58)	(reference)	
Present	13	0.31 (0.14–0.7)	0.21 (0.07–0.64)	2.90 (1.27–6.60)		0.08 (0.01–0.51)	0	2.99 (1.45–6.18)	
Pre-Transplant Status					0.03				0.12
VGPR/CR	23	0.62 (0.44–0.87)	0.62 (0.44–0.87)	(reference)		0.4 (0.24–0.68)	0.22 (0.09–0.53)	(reference)	
PR	21	0.47 (0.29–0.74)	0.19 (0.06–0.6)	2.56 (1.1–5.97)		0.14 (0.03–0.7)	0.14 (0.03–0.7)	1.66 (0.82–3.39)	

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