Stem Cell Mobilization and Autograft Minimal Residual Disease Negativity with Novel Induction Regimens in Multiple Myeloma

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Abstract

Autologous stem cell transplantation (ASCT) remains the standard of care for transplantation-eligible patients with multiple myeloma (MM). Bortezomib with lenalidomide and dexamethasone (VRD) is the most common triplet regimen for newly diagnosed MM in the United States. Carfilzomib with lenalidomide and dexamethasone (KRD) has shown promising efficacy and may supplant VRD. We compared stem cell yields and autograft minimal residual disease (MRD)-negativity after VRD and KRD induction. Deeper responses (ie, very good partial response or better) were more common with KRD. Precollection bone marrow (BM) cellularity, interval from the end of induction therapy to start of stem cell collection, and method of stem cell mobilization were similar for the 2 cohorts. Days to complete collection was greater with KRD (2.2 days, versus 1.81 days with VRD), which more often required ≥3 days of apheresis. Precollection viable CD34+ cell content was greater with VRD, as was collection yield (11.11 × 10^6, versus 9.19 × 10^6 with KRD). Collection failure (defined as <2 × 10^6 CD34+ cells/kg) was more frequent with KRD.
(5.4% versus .7% with VRD). The difference in stem cell yield between VRD and KRD is associated with the degree of lenalidomide exposure. Age ≥70 years predicted poorer collection for both cohorts. Stem cell autograft purity/MRD-negativity was higher with KRD (81.4%, versus 57.1% with VRD). For both cohorts, MRD-negativity was attained in a larger fraction of autografts than in precollection BM. For patients proceeding to ASCT, the time to neutrophil/platelet engraftment was comparable in the 2 study arms. In summary, our data indicate that KRD induces deeper clinical responses and greater autograft purity than VRD without compromising stem cell yield or post-transplantation engraftment kinetics.

**Keywords**

Minimal residual disease; Multiple myeloma; Autograft purity

**INTRODUCTION**

Multiple myeloma (MM) is a hematologic malignancy characterized by the abnormal proliferation of clonal plasma cells leading to end-organ damage. MM is incurable with conventional therapies, and progression of disease/relapse is inevitable for virtually all patients. The advent of novel therapeutic agents and advances in supportive care over the past 2 decades have significantly improved the median survival of patients with MM [1].

The depth of response to treatment is associated with clinical outcomes [2–5], and induction therapy with a 3-drug regimen, including a proteasome inhibitor and immunomodulatory agent, produces superior responses compared with 2-drug regimens [6,7]. The combination of bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (VRD) is the most frequently used triplet induction regimen for patients with newly diagnosed MM in the United States. The second-generation proteasome inhibitor carfilzomib (Kyprolis) is active in the relapsed setting [8,9] and when combined with lenalidomide and dexamethasone (KRD), generates deep responses in the induction setting [10,11].

Upfront high-dose therapy and autologous stem cell transplantation (ASCT) remains an important therapeutic option for transplantation-eligible patients with newly diagnosed MM [12–17]. For patients opting to forgo upfront ASCT, the collection and cryopreservation of peripheral blood stem cells for future use at the time of relapse is an essential consideration in the overall treatment plan, given the equivalent survival with the 2 approaches to date.

Contamination of stem cell autografts with MM cells or their precursors may contribute to relapse after ASCT [18]. Past attempts at purging autografts before ASCT showed no clear clinical benefit [19,20], but these efforts likely were limited by the low sensitivity of available testing and/or purging methodology. More recently, minimal residual disease (MRD) testing with flow cytometry-based or next-generation sequencing-based assays with the sensitivity to detect 1 myeloma cell in 10⁵ cells or more has emerged as an integral component of MM treatment response assessment [21], and MRD-negativity in both bone marrow (BM) and stem cell autografts has key prognostic implications. Achievement of MRD-negativity in the BM correlates with improved progression-free and overall survival.
[22,23], and the use of an MRD-negative graft is associated with improved outcomes after ASCT independent of BM MRD status pre-ASCT [24–26].

Owing to its promising clinical activity, KRD may ultimately supplant VRD as the preferred induction regimen for newly diagnosed MM in the United States and other countries with access to modern agents. Recent stem cell collection data from 30 patients receiving 4 to 8 cycles of KRD showed high rates of MRD-negative stem cell grafts [27]. To further define the outcomes of stem cell mobilization and collection after contemporary 3-drug induction regimens, we performed the first large-scale study (n = 275) comparing stem cell collection yields and autograft purity/MRD-negativity after induction therapy with VRD versus KRD.

METHODS

Patients

The study patients had newly diagnosed MM treated with VRD or KRD at Memorial Sloan Kettering Cancer Center between January 2014 and June 2019. Study data included patient demographics, myeloma-related characteristics, induction regimen and number of cycles received, response to induction therapy, pre-stem cell harvest parameters, mobilization parameters, preharvest BM and autograft MRD assessments, and post-transplantation engraftment information.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism (GraphPad Software, LA Jolla, CA). The unpaired t test, chi-square test, ANOVA, and Fisher’s exact test were used for comparative analyses.

RESULTS

Patient Demographics and Disease Characteristics

Table 1 summarizes the characteristics of the study cohort, which comprised 145 patients treated with VRD and 130 patients treated with KRD. There was no statistically significant difference in the patients’ median age or sex distribution between the 2 groups. IgG was the most common immunoglobulin isotype. The proportion of patients with high-risk cytogenetics was balanced between the 2 groups.

Response to Induction Therapy

As shown in Table 2, a higher fraction of patients treated with KRD achieved deeper responses, defined as very good partial response (VGPR) or better, with a higher percentage of complete response (CR) (22.8% for VRD versus 37.7% for KRD, \( P = .38 \)) and a lower percentage of partial response (PR) (35.9% for VRD versus 13.8% for KRD; \( P < .0001 \)). The rate of BM MRD-negativity at the time of preharvest testing was similar in the 2 arms (20.7% for VRD versus 28.4% for KRD; \( P = .82 \)). Patients in the KRD arm received an average of almost 1 additional cycle of therapy (5.9, versus 5.1 for VRD).
Table 3 summarizes the stem cell collection data for the VRD and KRD groups. There was no between-group difference in premobilization BM cellularity or the interval from the end of therapy to the start of stem cell collection. Regarding the method of stem cell mobilization, the majority of patients in both groups received a combination of granulocyte colony-stimulating factor (G-CSF) and plerixafor in accordance with institutional practice for patients with < 10% BM plasmacytosis on restaging BM biopsy before stem cell collection. Premobilization hematologic parameters showed higher WBC and hemoglobin values for the VRD arm and similar platelet values in the 2 arms. The VRD arm had higher WBC counts at the start of collection, required fewer days to meet our institutional collection target of ≥10 × 10^6 CD34+ cells/kg, and required ≥8 days of apheresis less often (20.7%, versus 37.6% for KRD; P = .155). Collection failure (defined as <2 × 10^6 CD34+ cells/kg collected over up to 4 consecutive days of apheresis) was rare but more frequent in the KRD arm. There was also a higher rate of suboptimal stem cell collection (defined as <5 × 10^6 CD34+ cells/kg collected over up to 4 consecutive days of apheresis) in the KRD arm.

The VRD patient who failed initial G-CSF and plerixafor-based stem cell collection also failed a second collection attempt following treatment with high-dose cyclophosphamide.

Of the 7 KRD patients who failed initial G-CSF- and plerixafor-based stem cell collection, 2 declined repeat collection, and 4 of the remaining 5 had successful repeat high-dose cyclophosphamide-based collection, with at least 2 × 10^6 CD34+ cells/kg obtained.

Patients in the VRD arm had a higher mean viable CD34+ cell content in the peripheral blood at the start of stem cell collection (107.9 ± 10.54 cells/μL, versus 62.3 ± 5.42 cells/μL in the KRD arm; P = .003) (Figure 1A), as well as a higher mean total stem cell yield (11.11 ± 0.5 CD34+ cells/kg versus 9.19 ± 0.38 CD34+ cells/kg; P = .002) (Figure 1B), including a higher mean stem cell yield on the first day of collection (8.38 ± .57 CD34+ cells/kg versus 6.28 ± .45 CD34+ cells/kg; P = .0035) (Figure 1C). In both arms, stem cell yield decreased with successive days of collection, with higher daily yields at each time point for VRD patients (Figure 1C). Advanced age (≥70 years) was a common factor predictive of lower stem cell yield in both arms (VRD: <60 years, 11.75 ± 5.83 cells/kg; 60-69 years, 10.92 ± 4.01 cells/kg; ≥70 years, 9.81 ± 3.95 cells/kg; KRD: <60 years, 10.15 ± 3.91 cells/kg; 60-69 years, 9.81 ± 3.95 cells/kg; ≥70 years, 6.31 ± 4.18 cells/kg) (Figure 1D).

The depth of response to induction therapy (ie, PR versus VGPR versus CR) before the start of stem cell collection had no significant effect on total stem cell yield (data not shown).

**MRD Assessments of Precollection BM and Autografts**

In a subset of study subjects, stem cell autograft purity/MRD-negativity (10^-5) assessed by 10-color flow cytometry [28] using fresh, noncryopreserved samples obtained on the first day of collection was higher in the KRD arm compared with the VRD arm (81.4% versus 57.1%; P = .25) (Figure 2A). In both arms, MRD-negativity was observed in a greater proportion of autografts than in precollection BM (VRD: 24.5% in BM versus 57.1% in autografts; KRD: 28.8% in BM versus 81.4% in autografts) (Figure 2A).
Post-Transplantation Engraftment Kinetics

For patients who proceeded to upfront transplantation, engraftment kinetics were comparable for the VRD and KRD arms, with an equivalent mean times to neutrophil engraftment, defined as an absolute neutrophil count of ≥5 × 10^9/L (500/mm^3) for 3 consecutive laboratory values obtained on different days (9.31 ± .78 days for VRD versus 9.44 ± .84 days for KRD) (Figure 2B), and platelet engraftment, defined as the date of the first of 3 consecutive platelet count values ≥20 × 10^9/L obtained on different days (19.96 ± 4.59 days for VRD versus 20.42 ± 4.95 days for KRD) (Figure 3B). All patients received conditioning chemotherapy with high-dose melphalan (VRD: 20.2% with 140 mg/m^2 and 79.8% with 200 mg/m^2; KRD: 11.1% with 140 mg/m^2 and 88.9% with 200 mg/m^2). Mean stem cell dose (CD34^+ cells/kg) was similar for the 2 arms (4.85 ± 1.25 CD34^+ cells/kg for VRD versus 4.46 ± 1.08 CD34^+ cells/kg for KRD).

Subgroup Analysis of Patients Receiving 6 Cycles of Induction Therapy

To correct for the disparity in the average number of induction cycles between the VRD and KRD arms, a subgroup analysis of patients receiving 6 cycles of induction therapy was performed. Patient demographics (Table 4) were similar to those of the entire study population (Table 1), as were responses to induction therapy, with a higher fraction of deep responses (≥VGPR) in the KRD arm (Table 5). As shown in Table 6 and Figure 3, premobilization hematologic parameters and stem cell collection data for patients receiving 6 cycles of induction therapy paralleled the trends seen in the entire study population, with VRD patients having a higher mean viable CD34^+ cell content at the start of stem cell collection (87.52 ± 11.82 cells/μL, versus 57.02 ± 5.23 cells/μL for KRD; P = .0168) (Figure 3A), with trends toward greater mean total stem cell yield (10.56 ± .75 CD34^+ cells/kg versus 8.88 ± .47 CD34^+ cells/kg; P = .045) (Figure 3B) and daily stem cell yield (Figure 3C). The KRD arm had higher rates of collection failure (ie, <2 × 10^6 CD34^+ cells/kg) and suboptimal total stem cell yield (ie, <5 × 10^6 CD34^+ cells/kg) (Table 6), as well as higher rates of BM and autograft MRD-negativity (30.8% in BM and 80.8% in autograft versus 22.9% in BM and 57.1% in autograft for VRD) (Figure 3D). For patients who underwent ASCT, neutrophil and platelet engraftment kinetics were comparable in the 2 arms (data not shown) and similar to those seen in the entire study population (Figure 2B).

Comparison of Patients Receiving 4 Cycles versus 6 Cycles of Induction Therapy

Compared with patients who received 6 cycles of induction therapy, those who received 4 cycles of induction therapy had a higher viable CD34^+ cell content at the start of stem cell collection (VRD: 129.3 ± 20.42 cells/μL for 4 cycles versus 84.77 ± 11.52 cells/μL for 6 cycles, P=.077; KRD: 93.5 ± 34.1 cells/μL for 4 cycles versus 57.02 ± 5.17 cells/μL for 6 cycles, P=.312) (Figure 4A) and greater total stem cell yield (VRD: 12.47 ± .94 CD34^+ cells/kg for 4 cycles versus 10.56 ± .73 for 6 cycles, P=.112; KRD: 9.87 ± .99 CD34^+ cells/kg for 4 cycles versus 9 ± .47 CD34^+ cells/kg for 6 cycles, P=.436) (Figure 4B). Collectively, patients who received 6 cycles of therapy had a higher fraction of autograft MRD-negativity (74.2%, versus 61.5% for 4 cycles).
Effect of Lenalidomide Dosing Schedule on Stem Cell Collection

VRD patients receiving 6 cycles of treatment on 21-day (VRD21; Revlimid on days 1 to 14 of each cycle) and 28-day (VRD28; Revlimid on days 1 to 21 of each cycle) schedules were compared to assess for the effect of lenalidomide exposure. VRD21 patients had a higher mean viable CD34+ cell content at the start of stem cell collection (102.8 ± 16.99 cells/μL, versus 60.5 ± 7.63 cells/μL for VRD28; *P* = .02) (Figure 5A). VRD21 patients also had a higher mean total stem cell yield (11.26 ± 1.06 CD34+ cells/kg versus 9.27 ± .63 CD34+ cells/kg for VRD28; *P* = .112) (Figure 5B). A comparison of VRD28 patients with patients receiving 6 cycles of KRD (Table 7) showed comparable mean CD34+ cell content at the start of stem cell collection (58.27 ± 7.45 cells/μL for VRD28 versus 57.02 ± 5.15 cells/μL for KRD; *P* = .892) (Figure 5C), as well as total stem cell yield (9.11 ± 0.59 CD34+ cells/kg versus 8.88 ± 0.47 CD34+ cells/kg; *P* = .707) (Figure 5D). As detailed in Table 8, a higher fraction of patients treated with KRD achieved deeper responses (VGPR or better) with a higher percentage of CR (41.1%, versus 33.4% for VRD28; *P* = .771) and a lower percentage of PR (10% versus 33.3%; *P* = .022).

DISCUSSION

In this study of 275 patients with newly diagnosed MM receiving up to 6 cycles of induction therapy with VRD or KRD, we show that KRD induces deeper clinical responses and greater stem cell graft purity than VRD without compromising stem cell yield or post-transplantation engraftment kinetics. In both the VRD and KRD arms, superior stem cell collection was associated with younger age, higher WBC count before collection or on the day of collection, higher premobilization hemoglobin, and higher viable CD34+ cell content in the peripheral blood at the start of stem cell collection.

Most patients in this study achieved stem cell yields that met or were close to our institutional goal of ≥10 × 10^6^ CD34+ cells/kg, although the mean total stem cell yield was lower in the KRD arm. There were no between-group differences in time off lenalidomide therapy before the start of collection, mobilization regimen, or preharvest BM cellularity. The average number of days to complete stem cell collection was slightly greater in the KRD arm, as was the fraction of patients requiring ≥3 days to complete collection.

Collection failure (ie, <2 × 10^6^ CD34+ cells/kg) was rare but more frequent in the KRD arm compared with the VRD arm. Of note, most cases of collection failure were salvaged with high-dose cyclophosphamide-based stem cell mobilization, with at least 2 × 10^6^ CD34+ cells/kg obtained during repeat stem cell collection. There was also a higher rate of suboptimal stem cell collection (ie, <5 × 10^6^ CD34+ cells/kg) in the KRD arm. Despite differences in stem cell collection between the VRD and KRD groups, post-transplantation neutrophil and platelet engraftment kinetics were comparable for patients who proceeded to ASCT, indicating an absence of detrimental effects on the quality of the autograft product after KRD.

Consistent with previous studies, patients treated with VRD and KRD achieved deep clinical responses (VGPR or better), with a higher proportion of KRD patients achieving a CR. Interestingly, MRD-negative status was attained in a larger proportion of autografts.
compared with precollection BM with both regimens. Patients treated with KRD had higher rates of autograft MRD-negativity, however. Although patients in the KRD arm received an average of almost 1 additional cycle of treatment, subgroup analysis of patients who received 6 cycles of VRD and KRD showed similar trends as seen in the overall study population, including higher rates of stem cell autograft MRD-negativity with KRD.

Lenalidomide-associated BM suppression reduces stem cell yield [29–32]. Administration of fewer cycles of lenalidomide-containing therapy is associated with a lower rate of collection failure [7,33]. Lenalidomide is typically administered for 21 days with carfilzomib and for 14 days with bortezomib. The higher cumulative dosing of lenalidomide with KRD is likely a predominant factor in the disparity in stem cell yields between the 2 study arms. Both bortezomib and carfilzomib can induce myelosuppression, including neutropenia and thrombocytopenia, but their effects on stem cell biology and collection yields remain to be defined.

The optimal number of induction cycles before stem cell collection has not been tested in randomized clinical trials but will be an important consideration in the near future, especially with the ongoing development of more myelosuppressive anti-CD38 monoclonal antibody-based 4-drug regimens. Our current institutional approach is to administer 6 cycles of induction to maximize disease response without compromising stem cell collection. Earlier stem cell collection likely would result in higher stem cell yields for more patients, but our study demonstrates the potential qualitative advantage of 6 cycles of induction therapy leading to greater autograft purity, which beyond serving as a marker of depth of response to initial treatment also may translate to improved outcomes after ASCT [24–26]. The clinical impact of MRD-negative autografts for the patients who proceeded to ASCT in this study remains unknown, owing to insufficient follow-up from the time of transplantation, and this warrants prospective monitoring.

In summary, extended induction therapy with up to 6 cycles of VRD and KRD does not impede successful stem cell mobilization and collection. Although both VRD and KRD are effective, KRD induces higher rates of deeper clinical responses and autograft MRD-negativity than VRD without impairing stem cell yield or engraftment after transplantation, despite a lower viable CD34+ content of samples at the time of stem cell mobilization, longer time to complete stem cell collection, and lower stem cell collection totals.

ACKNOWLEDGMENTS

The authors thank the clinical research staff, nurses, advanced practice providers, and physicians of the Adult Bone Marrow Transplant, Myeloma, Cell Therapy Laboratory, and Hematopathology Services at Memorial Sloan Kettering Cancer Center for assistance with sample procurement.

Financial disclosure: This work was supported in part by National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest statement: H.J.L. reports consultancy for Karyopharm and Pfizer and research support from Amgen, Spectrum, and Takeda. M.S. reports consultancy for McKinsey & Company, Angiocrine Bioscience, and Omeros Corporation and research funding from Angiocrine Bioscience. O.B.L. reports consultancy for MorphoSys. A.M.L. reports consultancy for Genmab, Bristol-Myers Squibb, and Takeda; honoraria from Genmab, Bristol-Myers Squibb, and Takeda; research funding from Genentech, Bristol Myers Squibb, and Janssen; and royalties from Serametrix. E.S. reports consultancy for Bristol-Myers Squibb, Fate Therapeutics, and Precision Biosciences
and research funding from Bristol-Myers Squibb. O.L. reports consultancy for Janssen, Merck, Pfizer, Takeda, Karyopharm, Amgen, Celgene, Binding Site, Adaptive, Cellectis, Glenmark, and Juno Therapeutics; honoraria from Janssen, Pfizer, Karyopharm, Amgen, Celgene, Binding Site, and Adaptive; and research funding from Janssen, Takeda, Amgen, Celgene, Glenmark, and Seattle Genetics. S.A.G. reports consultancy and research support from Celgene, Amgen, Takeda, Miltenyi, Novartis, and Sanofi. D.J.C reports research support from Genentech. The other authors have no conflicts of interest to report.

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Figure 1.
Stem cell collection after induction therapy with VRD and KRD. (A) Viable CD34⁺ stem cell content (cells/μL) at the start of stem cell collection. (B) Total stem cell yield. (C) Stem cell yield by day of collection. (D) Stem cell yield by age group for patients age <60, 60 to 69, and ≥70 years. n = 145 for VRD; n = 130 for KRD.
Figure 2.
MRD status and post-transplantation engraftment kinetics. (A) MRD status of precollection BM and stem cell autografts. n = 49 for VRD; n = 59 for KRD. (B) Days to absolute neutrophil count (ANC) and platelet (PLT) recovery after autologous stem cell transplantation. n = 114 for VRD; n = 63 for KRD.
Figure 3.
Stem cell collection after induction therapy with 6 cycles of VRD or KRD. (A) Viable CD34+ stem cell content (cells/μL) at the start of stem cell collection. (B) Total stem cell yield. (C) Stem cell yield by day of collection. (D) MRD status of precollection BM and stem cell autografts. In A-C, n = 39 for VRD; n = 83 for KRD. In D, n = 35 for VRD; n = 52 for KRD.
Figure 4.
Stem cell collection results after induction therapy with 4 cycles versus 6 cycles of VRD or KRD. (A) Viable CD34+ stem cell content (cells/μL) at the start of stem cell collection. (B) Total stem cell yield. (C) MRD status of stem cell autografts for all patients (VRD and KRD combined). In A and B, n = 63 for VRD 4; n = 42 for VRD 6; n = 12 for KRD 4; n = 90 for KRD 6. In C, n = 13 for 4 cycles; n = 66 for 6 cycles.
Figure 5.
Stem cell collection after induction therapy with 6 cycles of VRD on 21-day (VRD21) and 28-day (VRD28) cycles. (A) Viable CD34+ stem cell content (cells/μL) at the start of stem cell collection for VRD21 and VRD28. (B) Total stem cell yield for VRD21 and VRD28. (C) Viable CD34+ stem cell content (cells/μL) at the start of stem cell collection for VRD28 and KRD. (B) Total stem cell yield for VRD28 and KRD. In A and B, n = 25 for VRD21; n = 15 for VRD28. In C and D, n = 15 for VRD28; n = 90 for KRD.
### Table 1

Demographic Data and Disease Characteristics: All Patients

| Study Arm | Total Patients | Age, yr, median (range) | Sex, n | MM Subtype, n | ISS Stage, n | High-Risk Cytogenetics, n* |
|-----------|----------------|-------------------------|--------|---------------|--------------|----------------------------|
|           |                |                         | M      | F             | IgG          | IgA           | FLC | IgM | IgD | Other | I | II | III | Unknown |
| VRD       | 145            | 62 (25-80)              | 79     | 66            | 94           | 24            | 21  | 1   | 1   | 4     | 68 | 37 | 15  | 25        | 21 |
| KRD       | 130            | 61 (29-75)              | 75     | 55            | 79           | 30            | 17  | 0   | 1   | 3     | 74 | 27 | 11  | 18        | 24 |

ISS indicates International Staging System.

*\(t(4;14), t(14;20), 17p deletion.\)
Table 2

Response to Induction Therapy: All Patients

| Study Arm | Total Patients, n | Cycles, n, mean ± SD | CR, n (%) | VGPR, n (%) | <PR, n |
|-----------|-------------------|----------------------|-----------|-------------|--------|
|           |                   |                      | MRD+ | MRD− | MRD+ | MRD− | PR, n (%) | <PR, n |
| VRD       | 145               | 5.1 ± 1.35           | 12 (8.3) | 21 (14.5) | 51 (35.2) | 9 (6.2) | 52 (35.9) | 0       |
| KRD       | 130               | 5.9 ± .9             | 24 (18.5) | 25 (19.2) | 51 (39.2) | 12 (9.2) | 18 (13.8) | 0       |
Table 3

Stem Cell Collection Data: All Patients

| Parameter                                                                 | VRD Arm       | KRD Arm       |
|----------------------------------------------------------------------------|---------------|---------------|
| Precollection BM marrow cellularity, %, mean ± SD (P = 0.578)              | 38.5 ± 14.5   | 40.1 ± 14.2   |
| Time from end of induction therapy to start of collection, d, median (range) (P = 0.188) | 28 (8-100)    | 24 (9-195)    |
| G-CSF and plerixafor-based stem cell mobilization, n (%)                  | 135 (93.1)    | 126 (96.9)    |
| Chemotherapy-based stem cell mobilization                                 | 10 (6.9%)     | 4 (3.1%)      |
| Premobilization hematologic parameters, mean ± SD                         |               |               |
| WBC count (P = 0.0004)                                                    | 6 ± 2.5       | 4.9 ± 2.1     |
| Hemoglobin (P = 0.0002)                                                   | 12.3 ± 1.4    | 11.6 ± 1.3    |
| Platelet (P = 0.098)                                                      | 216 ± 71.5    | 203 ± 87.3    |
| WBC count at start of collection, mean ± SD (P = 0.02)                    | 49.75 ± 17.02 | 45.04 ± 18.58|
| Days to complete stem cell collection, mean (P = 0.003)                   | 1.81          | 2.20          |
| 1 day, (%)                                                                | 41.4          | 30            |
| 2 days, (%)                                                               | 37.9          | 32.3          |
| 3 days, (%)                                                               | 14.5          | 28.4          |
| 4 days, (%)                                                               | 6.2           | 9.2           |
| Collection failure (<2 × 10⁶ CD34⁺ cells/kg), n (%)                       | 1 (0.7)       | 7 (5.4)       |
| Suboptimal collection (<5 × 10⁶ CD34⁺ cells/kg), n (%)                    | 5 (3.4)       | 19 (14.6)     |
Table 4

Demographic Data and Disease Characteristics: 6 Induction Cycles

| Study Arm | Total Patients | Age, yr, median (range) | Sex, n | MM Subtype, n | ISS Stage, n | High-Risk Cytogenetics, n* |
|-----------|----------------|-------------------------|--------|---------------|--------------|---------------------------|
|           |                |                         | M      | F             | IgG          | IgA          | FLC | IgM | IgD | Other | I   | II  | III | Unknown |
| VRD       | 42             | 62 (25-80)              | 24     | 18            | 30           | 6            | 4   | 1   | 0   | 1     | 18  | 13  | 3   | 8       | 5   |
| KRD       | 90             | 61 (29-75)              | 50     | 40            | 59           | 20           | 9   | 0   | 1   | 1     | 54  | 16  | 7   | 13      | 18  |

* t(4;14), t(14,20), 17p deletion.
### Table 5

Response to Induction Therapy: 6 Induction Cycles

| Study Arm | Total Patients, Cycles, n | CR, n (%) | VGPR, n (%) | PR, n (%) | <PR, n (%) |
|-----------|--------------------------|-----------|-------------|-----------|------------|
|           |                          | MRD+      | MRD−        | MRD+      | MRD−       |           |
| VRD       | 42                       | 6         | 4 (9.5)     | 6 (14.3)  | 18 (42.9)  | 2 (4.8)   | 12 (28.6) | 0          |
| KRD       | 90                       | 6         | 20 (22.2)   | 17 (18.9) | 36 (40)    | 8 (8.9)   | 9 (10)    | 0          |
### Table 6

**Stem Cell Collection Data: 6 Induction Cycles**

| Parameter                                                                 | VRD Arm     | KRD Arm     |
|---------------------------------------------------------------------------|-------------|-------------|
| Precollection BM cellularity, %, mean ± SD ($P = .148$)                    | 35.8 ± 13.1 | 39.2 ± 15.1 |
| Time from end of induction therapy to start of collection, d, median (range) ($P = .479$) | 29 (10-100) | 24 (9-195)  |
| G-CSF and plerixafor-based stem cell mobilization, n (%)                  | 39 (92.9)   | 89 (98.9)   |
| Chemotherapy-based stem cell mobilization, n (%)                          | 3 (7.1)     | 1 (1.1)     |
| Premobilization hematologic parameters, mean ± SD                          |             |             |
| WBCs ($P = .03$)                                                          | 6 ± 2.7     | 4.9 ± 2.2   |
| Hemoglobin ($P = .0001$)                                                  | 12.5 ± 1.3  | 11.4 ± 1.1  |
| Platelets ($P = .498$)                                                    | 198.3 ± 63.9| 209.8 ± 89.3|
| WBC count at start of collection, mean ± SD ($P = .354$)                  | 48.9 ± 16.5 | 46 ± 18.9   |
| Days to complete stem cell collection, mean ($P = .024$)                  | 1.81        | 2.21        |
| 1 day, %                                                                  | 40          | 30          |
| 2 days, %                                                                 | 40          | 32.2        |
| 3 days, %                                                                 | 16.7        | 27.8        |
| 4 days, %                                                                 | 2.4         | 10          |
| Collection failures (<2 × 10^6 CD34+ cells/kg), n (%) ($P = .9$)           | 1 (2.4)     | 6 (6.7)     |
| Suboptimal collection (<5 × 10^6 CD34+ cells/kg), n (%)                   | 2 (4.8)     | 16 (17.8)   |
Table 7
Patient Demographics and Disease Characteristics (VRD28 vs KRD)

| Study Arm | Total Patients | Age, yr, median (range) | Sex, n | MM Subtype, n | ISS Stage, n | High-Risk Cytogenetics, n* |
|-----------|----------------|-------------------------|--------|---------------|--------------|---------------------------|
|           |                |                         |        | M | F | IgG | IgA | FLC | IgM | IgD | Other | I   | II  | III | Unknown |
| VRD28     | 15             | 66 (53-74)              | 7      | 8 | 9 | 4   | 2   | 0   | 0   | 0   | 7   | 6   | 1   | 1       | 3       |
| KRD       | 90             | 61 (29-75)              | 50     | 40| 59| 20  | 9   | 0   | 1   | 1   | 54  | 16  | 7   | 13      | 18      |

* t(4;14), t(14,20), 17p deletion.
| Study Arm | Total Patients, n | Cycles, n | CR, n (%) | VGPR, n (%) | PR, n (%) | <PR, n |
|-----------|------------------|-----------|-----------|-------------|-----------|--------|
| VRD28     | 15               | 6         | 1 (6.7)   | 4 (26.7)    | 4 (26.7)  | 1 (6.7) |
|           |                  |           | MRD+      | MRD+        | MRD+      | MRD+   |
| KRD       | 90               | 6         | 20 (22.2)| 17 (18.9)   | 36 (40)   | 9 (10) |
|           |                  |           | MRD+      | MRD+        | MRD+      | MRD+   |

Table 8

Response to Induction Therapy (VRD28 versus KRD)