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Hematopoietic progenitor cell collection after autologous transplant for multiple myeloma: low platelet count predicts for poor collection and sole use of resulting graft enhances risk of myelodysplasia

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Abstract

Collection of hematopoietic progenitor cells (HPC) after previous autologous hematopoietic progenitor cell transplant (aHCT) was studied in 221 patients with multiple myeloma (MM). With a total of 333 collections, the median number of CD34 cells collected was 4.7×10^6 CD34 + cells/kg, and 74% of the patients collected $\geq 2.5 \times 10^6$ CD34 + cells/kg. Among 26 variables examined, the strongest predictor for poor collection was a platelet count $<100 \times 10^6$/l before mobilization ($P<0.001$). A subsequent aHCT was performed in 154 of the 221 patients. Sole use of HPC procured after aHCT in 86 patients was associated with delayed platelet recovery ($P<0.001$) and linked to development of myelodysplastic syndrome (MDS)-associated cytogenetic abnormalities (MDS-CA; $P = 0.027$, odds ratio (OR) 10.34) and a tendency towards clinical MDS/acute myeloid leukemia (AML; $P = 0.091$, OR 3.57). However, treatment-related mortality ($P = 0.766$) and time to absolute neutrophil count recovery $\geq 0.5 \times 10^9$/l ($P = 0.879$) were similar to when a pre-aHCT graft was used. Indeed, adding HPC collected before any aHCT neutralized the risk of MDS-CA or MDS/AML. Therefore, we advise generous initial HPC collection to broaden the salvage armamentarium for patients with MM.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: MCF, BB and XP. Administrative support: MCF and BB. Provision of study material or patients: MCF, ER, LNT, BB, JS and CJH. Collection and assembly of data: XP and LNT. Data analysis and interpretation: XP, ER, MCF and BB.

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Keywords

HPC collection; plerixafor; myeloma; transplant; MDS

INTRODUCTION

Overall survival in multiple myeloma (MM) has improved significantly over the last 30 years,[1] because of autologous hematopoietic progenitor cell (HPC) transplant (aHCT)-supported high-dose therapy[2] and the availability of novel agents, especially when incorporated into primary aHCT protocols.[2,3] In the setting of relapsed MM, further aHCT salvage is superior to conventional chemotherapy.[4] Unfortunately, the current practice of collecting only sufficient HPC to support the planned initial aHCT leaves many relapsing patients without cryopreserved HPC. The variables determining the feasibility of HPC collection after prior aHCT were therefore investigated along with engraftment potential of such HPC following a salvage aHCT. The increasing concern about the risk of secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) after MM therapy[5-7] prompted an investigation of variables linked to MDS-related cytogenetic abnormalities (MDS-CA) and clinical MDS/AML after the use of HPC collected following previous transplantation.

PATIENTS AND METHODS

Patients

Records of patients who had received prior aHCT for symptomatic MM between January 2000 and January 2012 were reviewed to identify those in whom a post-aHCT HPC collection was attempted. Patient characteristics and mobilization regimens are shown in Table 1. Mobilization regimens called for the subcutaneous administration of filgrastim (granulocyte colony-stimulating growth factor, 5 μg/kg) twice a day. Plerixafor, added for 56 patients in a total of 76 collections, was dosed subcutaneously at 240 μg/kg when the estimated glomerular filtration rate exceeded 50 mg/min per 1.73 m^2 (cap, 40 000 μg) and 160 μg/kg (cap, 27 000 μg) in case of lower glomerular filtration rate.

Methods

Laboratory data—We defined premobilization blood cell counts as the complete blood count obtained closest to the start of the mobilization regimen and no more than 30 days before the start of HPC collection. The same rule applied to bone marrow-derived data and to all other laboratory measurements. Metaphase karyotyping for detecting CA, typical of MM (MM-CA) or MDS (MDS-CA),[6,8,9] was part of each bone marrow examination. All MM-CA or MDS-CA determinations were made by one of the authors (JS, BB and XP). As bone marrow morphology can be altered by MM therapy[10] and MDS-CA can be transient or even not associated with clinically evident MDS,[6] we defined clinical MDS/AML as the condition for which specific MDS/AML therapy was required and administered.[10]

Apheresis—HPC collection was performed using a COBE Spectra apheresis machine (TerumoBCT, Lakewood, CO, USA) to perform large volume leukapheresis (30 l

processed) through a central venous catheter using 1000 ml anticoagulant citrate dextrose and 5000 units heparin for anticoagulation at an inlet: anti-coagulant ratio of 31:1 and an inlet flow rate of 150 ml/min with anticoagulant infused at 5 ml/min. Collection flow rate was set at 1.5 ml/min and 10 ml of anticoagulant citrate dextrose was added to the component at processed volumes of 10, 20 and 30 l. An infusion of 2 g calcium chloride in 250 ml normal saline (0.9% sodium chloride) ran at 85 ml/h. Collection was guided by our predictive formula.[11] Collection was started when the predicted collection was at least 0.5×10^6 CD34+ cells/kg and continued until the goal was met or the daily collection contained $<0.5 \times 10^6$ CD34+ cells/kg.

Flow cytometry—Specimens drawn 1 h before apheresis were used to quantify CD34+ cells/μl peripheral blood using the BD Procount kit (BD Biosciences, San Jose, CA, USA) on a FACSCalibur (BD Biosciences). These CD34+ values were used in our predictive formula.[9] CD34+ cells collected by apheresis were quantified by flow cytometry using the International Society for Hematotherapy and Graft Engineering protocol.[12]

Time to engraftment—The day of HPC infusion was designated day 0. Neutrophil engraftment was defined as the second consecutive day of absolute neutrophil count $\geq 0.5 \times 10^9$/l. Platelet engraftment to $\geq 20 \times 10^9$/l and to $\geq 50 \times 10^9$/l was defined as the second consecutive day that an untransfused platelet count at or above these levels was documented.

Statistical methods—Differences between clinical and laboratory variables among selected patient populations were compared using two-tailed Student's *t*-tests, Mann-Whitney *U*-tests and univariate or multivariate analyses of binomial logistic regression where appropriate. For all analyses, $P \leq 0.05$ was considered statistically significant, while values >0.05 and ≤ 0.1 were considered as tending to statistical significance.

RESULTS

Patient characteristics

We identified 221 MM patients mobilized after at least one prior aHCT, for a total of 333 collections. The median age was 56 years (range 29–82) and 65% were males; 112 had one prior aHCT, 88 had two, and 21 had three or more such interventions (Table 1). Prior relapses ranged from 1 to 13 (median, 2), and the median time from last aHCT was 4.2 years (range 0.1–12.4). Metaphase cytogenetics data were available for 209 of 333 collections (64%). Of these, 133 (64%) were normal, 72 (34%) were deemed MM-CA and 4 (2%) MDS-CA. MDS-CA at any time before a collection was documented in 22 of 333 collections (7%; Table 1). Data on bone marrow cellularity, morphology and degree of plasma cell infiltration were available within 1-month before mobilization for 217 of 333 collections (65%). MDS morphology was evident in 36 of 217 (16%) cases.

The median number of HPC collected before the first aHCT was 12.5×10^6 CD34+ /kg (range 0.7–87.6), which was accomplished in a median of 3 days (range 1–8). After aHCT, a median of 4.7×10^6 CD34+ /kg (range 0.07–31.9) HPC was collected in a median of 4 days (range 1–10) with 74% (248/333) of the collections having $\geq 2.5 \times 10^6$ CD34+ cells/kg. Complete mobilization regimen information was available in 308 of 333 apheresis

procedures (Table 2). Among the mobilization regimens listed in Table 1, conventional chemotherapy and granulocyte colony-stimulating growth factor effected the highest yield (median of 6.84×10^6 CD34+ cells/kg, range 0.2–31.9, $P<0.001$, Supplementary Table 1) and sole use of growth factors the lowest CD34 yield (median of 3.01×10^6 CD34+ cells/kg collected, range 0.2–19.8, $P<0.001$, Supplementary Table 1). Plerixafor, added in 56 patients for a total of 75 collections, improved the CD34 yield in patients with a poor collection previously ($<2.5 \times 10^6$ CD34+ cells/kg), increasing the median CD34 count from 1.83×10^6 CD34+ cells/kg to 3.43×10^6 CD34+ cells/kg ($P<0.001$). Plerixafor's efficacy was not affected by glomerular filtration rate ($P = 0.902$).

Factors related to HPC yield and engraftment times after subsequent aHCT

Other authors have suggested a minimum of 2.5×10^6 CD34+ cells/kg are required for successful engraftment.[13,14] We therefore used this number as a collection threshold in determining mobilization variables. In univariate analysis, poor collection was linked to sole use of growth factors without chemotherapy ($P<0.001$, odds ratio (OR) 2.77), pre-collection hemoglobin <11 g/dl ($P = 0.032$, OR 1.75) and platelet count $<100 \times 10^9$/l ($P<0.001$, OR 2.43); participation in Total Therapy protocols ($P = 0.022$, OR 2.14), female sex ($P = 0.047$, OR 1.66) and low albumin <3.5 g/dl ($P = 0.003$, OR 2.08) were additional adverse features (Table 2a). Conversely, higher HPC yields were linked to the use of chemotherapy in the mobilization regimen ($P<0.001$, OR 0.38), the presence of MM-CA before mobilization ($P<0.001$, OR 0.06) and bone marrow cellularity>80% ($P = 0.029$, OR 0.10). In multivariate analysis, the only surviving adverse variables were platelet count $<100 \times 10^9$/l ($P = 0.007$, OR 2.56) and mobilization solely with growth factors ($P = 0.030$, OR 2.34); the favorable effect of the presence of MM-CA is not understood ($P = 0.042$, OR 0.06).

Of the 221 patients with HPC collections, 154 underwent a subsequent aHCT; the aHCT regimens are depicted in Supplementary Table 2. The source of HPC in the graft was grouped as follows for analysis: 44 patients were grafted with HPC solely procured before the initial aHCT, 86 patients were grafted solely with cells procured after aHCT and 24 received a combination of both ('before', 'after' and 'both' groups, respectively; Table 3). The median numbers of infused HPC were 4.95, 4.49 and 4.36×10^6 Although CD34+ cells/kg in the three groups, respectively. neutrophil recovery to $\geq 0.5 \times 10^9$/l and platelet recovery $\geq 20 \times 10^9$/l was similar among the three groups, platelet engraftment $\geq 50 \times 10^9$/l occurred at medians of 15, 20 and 15 days, respectively, with the longest time seen in the 'after' group ($P<0.001$; Table 3). Neither bone marrow morphology, CA before aHCT, nor time elapsed from the most recent collection showed a statistical correlation with neutrophil or platelet engraftment times (data not shown). No statistically significant differences were noted in treatment-related mortality for the three groups (5%, 3.5% and 0% for 'before', 'after' and 'both' groups, respectively; $P = 0.766$). Median overall survival and progression-free survival after aHCT was 14.7 and 5.8 months, with no statistical difference between the three graft groups ($P = 0.167$ and $P = 0.238$ for overall survival and progression-free survival, respectively).

MDS-CA and clinical MDS/AML after HPC collection

Of the 221 patients in this study, MDS-CA developed in 11% (25/221), while clinical MDS/AML developed in 5% (12/221) after HPC collection. MDS-CA encounters are summarized in Supplementary Table 3.

All factors evaluated for prediction of the collection yield as well as the number of CD34+ cells collected were analyzed for their correlation with development of MDS-CA and clinical MDS/AML after HPC collection. MDS-CA development after HPC collection was linked in univariate analysis to the presence of MDS-CA within 1-month before mobilization ($P = 0.009$, OR 20.6), presence of MDS-CA at any time before mobilization ($P<0.001$, OR 9.70), hemoglobin <11 g/dl ($P = 0.016$, OR 2.74), albumin <3.5 g/dl ($P = 0.030$, OR 2.27) and poor collection (<2.5×10^6 CD34+ cells/kg; $P = 0.035$, OR 2.59). In multivariate analysis, only the presence of MDS-CA at any time before mobilization and albumin concentration <3.5 g/dl were statistically significant ($P<0.001$, OR 11.6 and $P = 0.025$, OR 3.13; Table 4).

As to clinical MDS/AML, presence of MDS-CA at any time before mobilization ($P = 0.001$, OR 5.88) and albumin <3.5 g/dl ($P = 0.013$, OR 3.56) were significant in univariate analysis. In multivariate analysis, albumin <3.5 g/dl and MDS-CA present at any time before mobilization showed a statistical tendency towards significance ($P = 0.058$, OR 5.18 and $P = 0.076$, OR 3.30; Table 4).

MDS-CA and clinical MDS/AML after aHCT

Development of MDS-CA and clinical MDS/AML after aHCT was seen in 8% (13/154) and 6% (10/154), respectively. All factors examined for engraftment times were used for statistical analysis. The use of a graft consisting solely of CD34+ cells procured after HCT was the only factor significantly related to the subsequent development of MDS-CA ($P = 0.027$, OR 10.34) and a tendency towards the development of clinical MDS/AML was also seen ($P = 0.091$, OR 3.57).

DISCUSSION

Mobilization and collection following a previous aHCT is clearly feasible, as the majority of patients (74%) here collected a sufficient number of CD34+ cells (≥2.5×10^6/kg) for at least one aHCT. The pre-mobilization platelet count proved to be the most important factor in predicting a poor collection. This finding is in accord with earlier work from our institution in a similar population of previously transplanted patients.[15] Platelet count before mobilization has also been found to be predictive of successful HPC collection in a study at our institution of elderly patients (>70 years) without a history of aHCT.[16] An explanation for this finding may be the close relationship of megakaryopoietic commitment to the totipotent stem cell described in a novel model of sequential hematopoietic lineage commitment.[17] Also the association between the platelet count and the number of CD34+ cells collected in this study could reflect a change in the ‘cytokine microenvironment’ of the bone marrow through chemotherapy[18,19] and the plasma cell niche, of which the megakaryocytes are a functional part.[20] Another possible explanation is the potential co-

existence of treatment-related MDS. Although a poor collection was linked to subsequent development of MDS-CA in our series of patients ($P = 0.035$, OR 2.59), a low platelet count did not predict development of MDS (data not shown).

Prior Total Therapy protocol participation correlated with poor collection ($P = 0.022$, OR 2.14), due in part to the preferential use of growth factors alone for mobilization in this patient subset (18/48 v 53/260 for the remainder, $P = 0.01$). We found the use of growth factors alone for HPC mobilization predicted a 'poor' collection ($P = 0.001$, OR 2.77). Although we have no explanation for the improved HPC collection seen here in the presence of MM-CA ($P<0.001$, OR 16.67), one may speculate that the higher proliferative capacity of MM with MM-CA (via thrombopoiesis-promoting IL6)[21] and its greater stromal cell independence[22,23] may both facilitate normal hematopoietic niche egress.[24,25] Patients with either anemia (Hb <11 g/dl) or hypoalbulinemia (<3.5 g/dl) tended to be poor collectors ($P = 0.032$, OR 1.75, $P = 0.003$, OR 2.08, respectively). Given the effect of red blood cells on plasma volume and blood viscosity as well as the effect of hypoalbulinemia on blood viscosity[26] and poor collection,[16,27] it could be that these two factors have an immediate effect on the 'physics' of the mononuclear cell layer formation during apheresis. Bone marrow cellularity was associated in two ways with the number of CD34+ collected. Specifically, those with a cellularity <30% had a tendency towards poor collection ($P = 0.066$, OR 1.86), whereas those with a cellularity >80% were associated with good collection ($P = 0.029$, OR 0.10), perhaps reflecting the ability of stroma to support hematopoietic cells and therefore impact HPC mobilization.

The linkage of poor HPC collection after prior aHCT to female sex is in accord with large series of HPC collections in both healthy donors[28] and patients with hematological malignancies.[29] Chemotherapy-based mobilization proved to be most efficient in our cohort of patients, as has been shown in other settings.[13,16] This implies that the basic clinical and biological facts that govern HPC mobilization[30] remain the same regardless of previous treatment history.

Mobilization regimens did not show a correlation with subsequent MDS-CA development or clinical MDS/AML, including plerixafor, which has recently been reported to predispose patients to clinical MDS/AML.[31] Plerixafor performed well in patients with a history of poor collection ($<2.5 \times 10^6$ CD34+ cells/kg; 1.83 vs 3.43 $\times 10^6$/kg, $P <0.001$), in agreement with experience in non-previously-transplanted patients.[32] Impaired renal function did not affect the ability of plerixafor to enhance collection.

In this series, as expected, the presence of MDS-CA within a month before mobilization ($P = 0.009$, OR 20.6) and especially the presence of MDS-CA at any time before mobilization ($P<0.001$, OR 9.70) correlated with the subsequent development of MDS-CA and clinical MDS/AML in both univariate and multivariate analyses (Table 4). We found poor collection ($<2.5 \times 10^6$ CD34+ cells/kg; $P = 0.035$, OR 2.59) was related to the development of subsequent MDS-CA (Table 4), as previously reported.[6] The presence of anemia (hemoglobin <11 g/dl; $P = 0.016$, OR 2.74) was also related to subsequent MDS-CA development, perhaps tied to the recent observation of erythropoietin gene promoter polymorphisms to the development of secondary MDS in MM patients.[33] Albumin

concentration <3.5 g/dl was predictive not only of MDS-CA but also of clinical MDS/AML, and a trend was noted for elevated beta-2 microglobulin (Table 4). These two factors are markers of more aggressive MM. Beta-2 microglobulin >5.5 g/dl has been shown to be related to the development of both MDS-CA and clinical MDS/AML in MM.[10]

Use of an HPC graft consisting of cells procured after aHCT either alone or combined with cells collected before transplant did not affect treatment-related mortality of aHCT when compared with a graft consisting only of cells collected before the first aHCT. The delayed platelet engraftment seen in the 'after' vs 'before' (21 vs 15 days, $P<0.001$), and the 'after' vs 'both' groups (21 vs 15 days, $P = 0.003$) is in agreement with previous findings.[15] HPC procured after an aHCT are functionally inferior to HPC collected early in the course of the disease before cumulative damage to the bone marrow from repeated or intense chemotherapy develops. The use of these cells alone as a graft, without the addition of cells collected earlier in the course of therapy, was the only factor in our data predisposing to MDS-CA development after aHCT ($P = 0.027$, OR 10.34), and a statistical tendency for the development of clinical MDS/AML was also noted ($P = 0.091$, OR 3.57). Since the effect of a salvage aHCT in MM is well established,[4,34,35] we suggest that adequate HPC for at least two aHCT be collected upfront in MM, especially if the findings of this study where the sole use of HPC procured after a previous aHCT effected MDS-CA and clinical MDS/AML development are confirmed by other studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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REFERENCES

1. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med. 2004; 351:1860–1873. [PubMed: 15509819]
2. Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med. 2006; 354:1021–1030. [PubMed: 16525139]
3. Nair B, van Rhee F, Shaughnessy JD Jr, Anaissie E, Szymonifka J, Hoering A, et al. Superior results of Total Therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with VRD maintenance. Blood. 2010; 115:4168–4173. [PubMed: 20124509]
4. Cook G, Liakopoulou E, Pearce R, Cavet J, Morgan GJ, Kirkland K, et al. Factors influencing the outcome of a second autologous stem cell transplant (ASCT) in relapsed multiple myeloma: a study from the British Society of Blood and Marrow Transplantation Registry. Biol Blood Marrow Transplant. 2011; 17:1638–1645. [PubMed: 21565277]
5. Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med. 2012; 366:1759–1769. [PubMed: 22571200]
6. Barlogie B, Tricot G, Haessler J, van Rhee F, Cottler-Fox M, Anaissie E, et al. Cytogenetically defined myelodysplasia after melphalan-based autotransplantation for multiple myeloma linked to

poor hematopoietic stem-cell mobilization: the Arkansas experience in more than 3,000 patients treated since 1989. Blood. 2008; 111:94–100. [PubMed: 17895401]

7. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012; 366:1770–1781. [PubMed: 22571201]
8. Debes-Marun CS, Dewald GW, Bryant S, Picken E, Santana-Davila R, Gonzalez-Paz N, et al. Chromosome abnormalities clustering and its implications for pathogenesis and prognosis in myeloma. Leukemia. 2003; 17:427–436. [PubMed: 12592343]
9. Schoch C, Kern W, Schnittger S, Hiddemann W, Haferlach T. Karyotype is an independent prognostic parameter in therapy-related acute myeloid leukemia (t-AML): an analysis of 93 patients with t-AML in comparison to 1091 patients with de novo AML. Leukemia. 2004; 18:120–125. [PubMed: 14586477]
10. Usmani SZ, Sawyer J, Rosenthal A, Cottler-Fox M, Epstein J, Yaccoby S, et al. Risk factors for MDS and acute leukemia following total therapy 2 and 3 for multiple myeloma. Blood. 2013; 121:4753–4757. [PubMed: 23603914]
11. Rosenbaum ER, O'Connell B, Cottler-Fox M. Validation of a formula for predicting daily CD34(+) cell collection by leukapheresis. Cytotherapy. 2012; 14:461–466. [PubMed: 22277012]
12. Keeney M, Chin-Yee I, Weir K, Popma J, Nayar R, Sutherland DR, International Society of Hematotherapy and Graft Engineering. Single platform flow cytometric absolute CD34+ cell counts based on the ISHAGE guidelines. Cytometry. 1998; 34:61–70. [PubMed: 9579602]
13. Bensinger W, Appelbaum F, Rowley S, Storb R, Sanders J, Lilleby K, et al. Factors that influence collection and engraftment of autologous peripheral-blood stem cells. J Clin Oncol. 1995; 13:2547–2555. [PubMed: 7595706]
14. Weaver CH, Hazelton B, Birch R, Palmer P, Allen C, Schwartzberg L, et al. An analysis of engraftment kinetics as a function of the CD34 content of peripheral blood progenitor cell collections in 692 patients after the administration of myeloablative chemotherapy. Blood. 1995; 86:3961–3969. [PubMed: 7579367]
15. Singhal S, Mehta J, Desikan K, Siegel D, Singh J, Munshi N, et al. Collection of peripheral blood stem cells after a preceding autograft: unfavorable effect of prior interferon-alpha therapy. Bone Marrow Transplant. 1999; 24:13–17. [PubMed: 10435728]
16. Morris CL, Siegel E, Barlogie B, Cottler-Fox M, Lin P, Fassas A, et al. Mobilization of CD34+ cells in elderly patients (>/ = 70 years) with multiple myeloma: influence of age, prior therapy, platelet count and mobilization regimen. Br J Haematol. 2003; 120:413–423. [PubMed: 12580955]
17. Zhu J, Emerson SG. Hematopoietic cytokines, transcription factors and lineage commitment. Oncogene. 2002; 21:3295–3313. [PubMed: 12032771]
18. Bautz F, Rafii S, Kanz L, Mohle R. Expression and secretion of vascular endothelial growth factor-A by cytokine-stimulated hematopoietic progenitor cells. Possible role in the hematopoietic microenvironment. Exp Hematol. 2000; 28:700–706. [PubMed: 10880756]
19. Wickenhauser C, Lorenzen J, Thiele J, Hillienhof A, Jungheim K, Schmitz B, et al. Secretion of cytokines (interleukins-1 alpha, −3, and −6 and granulocyte-macrophage colony-stimulating factor) by normal human bone marrow mega-karyocytes. Blood. 1995; 85:685–691. [PubMed: 7833472]
20. Winter O, Moser K, Mohr E, Zotos D, Kaminski H, Szyska M, et al. Megakaryocytes constitute a functional component of a plasma cell niche in the bone marrow. Blood. 2010; 116:1867–1875. [PubMed: 20538807]
21. Kaser A, Brandacher G, Steurer W, Kaser S, Offner FA, Zoller H, et al. Interleukin-6 stimulates thrombopoiesis through thrombopoietin: role in inflammatory thrombocytosis. Blood. 2001; 98:2720–2725. [PubMed: 11675343]
22. Barlogie B, Shaughnessy J, Tricot G, Jacobson J, Zangari M, Anaissie E, et al. Treatment of multiple myeloma. Blood. 2004; 103:20–32. [PubMed: 12969978]
23. Shaughnessy J, Jacobson J, Sawyer J, McCoy J, Fassas A, Zhan F, et al. Continuous absence of metaphase-defined cytogenetic abnormalities, especially of chromosome 13 and hypodiploidy, ensures long-term survival in multiple myeloma treated with Total Therapy I: interpretation in the context of global gene expression. Blood. 2003; 101:3849–3856. [PubMed: 12531801]

24. Noll JE, Williams SA, Purton LE, Zannettino AC. Tug of war in the haematopoietic stem cell niche: do myeloma plasma cells compete for the HSC niche? Blood Cancer J. 2012; 2:e91. [PubMed: 22983434]
25. Dar A, Schajnovitz A, Lapid K, Kalinkovich A, Itkin T, Ludin A, et al. Rapid mobilization of hematopoietic progenitors by AMD3100 and catecholamines is mediated by CXCR4-dependent SDF-1 release from bone marrow stromal cells. Leukemia. 2011; 25:1286–1296. [PubMed: 21494253]
26. Joles JA, Willekes-Koolschijn N, Koomans HA. Hypoalbuminemia causes high blood viscosity by increasing red cell lysophosphatidylcholine. Kidney Int. 1997; 52:761–770. [PubMed: 9291198]
27. Ford CD, Pace N, Lehman C. Factors affecting the efficiency of collection of CD34-positive peripheral blood cells by a blood cell separator. Transfusion. 1998; 38:1046–1050. [PubMed: 9838936]
28. Vasu S, Leitman SF, Tisdale JF, Hsieh MM, Childs RW, Barrett AJ, et al. Donor demographic and laboratory predictors of allogeneic peripheral blood stem cell mobilization in an ethnically diverse population. Blood. 2008; 112:2092–2100. [PubMed: 18523146]
29. Zhang C, Chen X, Zhang X, Gao L, Kong P, Wang Q, et al. Mobilization of peripheral blood stem cells for autologous transplantation patients with hematological malignancies: influence of disease, mobilization method, age and sex. Transfusion Apheresis Sci. 2008; 39:21–28.
30. Pelus LM, Fukuda S. Chemokine-mobilized adult stem cells; defining a better hematopoietic graft. Leukemia. 2008; 22:466–473. [PubMed: 17972941]
31. Deol A, Abrams J, Masood A, Al-Kadhimi Z, Abidi MH, Ayash L, et al. Long-term follow up of patients proceeding to transplant using plerixafor mobilized stem cells and incidence of secondary myelodysplastic syndrome/AML. Bone Marrow Transplantation. 2013 e-pub ahead of print 11 March 2013; PMID: 23474805.
32. Hubel K, Fresen MM, Apperley JF, Basak GW, Douglas KW, Gabriel IH, et al. European data on stem cell mobilization with plerixafor in non-Hodgkin's lymphoma, Hodgkin's lymphoma and multiple myeloma patients. A subgroup analysis of the European Consortium of stem cell mobilization. Bone Marrow Transplant. 2012; 47:1046–1050. [PubMed: 22080971]
33. Landgren O, Ma W, Kyle RA, Rajkumar SV, Korde N, Albitar M. Polymorphism of the erythropoietin gene promotor and the development of myelodysplastic syndromes subsequent to multiple myeloma. Leukemia. 2012; 26:844–845. [PubMed: 21926963]
34. Barlogie B, Anaissie E, van Rhee F, Pineda-Roman M, Zangari M, Shaughnessy J, et al. The Arkansas approach to therapy of patients with multiple myeloma. Best practice & research. Clin Haematol. 2007; 20:761–781.
35. Shah N, Ahmed F, Bashir Q, Qureshi S, Dinh Y, Rondon G, et al. Durable remission with salvage second autotransplants in patients with multiple myeloma. Cancer. 2012; 118:3549–3555. [PubMed: 22086552]

Table 1

Patient characteristics and mobilization regimens

Patient characteristics (general)	N = *221 (%)*
Sex (male)	144 (65%)
Age (median (range)) in years	56 (29–82)
Caucasian	201 (91%)
More than two relapses	115 (52%)
More than two prior aHCTs	21 (9%)
Total Therapy protocol participation	28 (13%)
CD34 count of initial HPC collection × 10^6/kg (median (range))	12.5 (0.7–87.6)
Days of initial HPC collection (median (range))	3 (1–8)
Patient characteristics (specific before mobilization)	N = *333 (%)*
Beta-2 microglobulin >3.5mg/l (*n/N*)	115/331 (35%)
Albumin <3.5g/dl (*n/N*)	180/333 (54%)
CRP >6mg/l (*n/N*)	190/275 (69%)
Abnormal metaphase cytogenetics within one month from mobilization	76/209 (36%)
MM-CA within 1 month from mobilization	72/209 (34%)
MDS-CA within 1 month from mobilization	4/209 (2%)
MDS-CA present at any time before mobilization	22/333 (7%)
Plasma cell infiltration >60% (*n/N*)	30/217 (14%)
Creatinine >2mg/dl (*n/N*)	18/333 (5%)
Time from last aHCT to mobilization (median (range)) in years	4.2 (0–12.4)
Number of collections according to the number of prior aHCTs	(n/N) (%)
One	181/333 (54%)
Two	126/333 (38%)
Three or more	26/333 (8%)
Mobilization regimens	N = *308*
No chemotherapy	*n* = 142
G-CSF	32
G-CSF + plerixafor	63
GM-CSF + G-CSF + Epo	39
G-CSF + Epo	4
GM-CSF + Epo	1
G-CSF + GM-CSF	3
Chemotherapy + GCSF ± other	*n* = 166
VDT-PACE + G-CSF	90
VDT-PACE + G-CSF + plerixafor	12
VDT-ACE + G-CSF	8
DT-PACE + G-CSF	30
DT-PACE + GM-CSF	1

E + G-CSF	5
VDT-PACE + PEG-G-CSF	1
CE + G-CSF	7
CE + G-CSF + GM-CSF + Epo	2
C + G-CSF + GM-CSF + Epo	2
DCEP + G-CSF	4
MEL100 + VDT-PACE + G-CSF	1
BEAM + G-CSF + plerixafor	1
PACMED + G-CSF	2

Abbreviations: ACE, adriamycin, cyclophosphamide, etoposide; aHCT, autologous hematopoietic progenitor cell transplant; BEAM, carmustine, etoposide, cytarabine, melphalan; C, cyclophosphamide; CA, cytogenetic abnormalities; CE, cyclophosphamide, etoposide; CRP, C-reactive protein; DCEP, dexamethasone, cyclophosphamide, etoposide, cisplatin; DT, dex–amethasone, thalidomide; E, etoposide; Epo, erythropoietin; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HPC, hematopoietic progenitor cell; MEL100, 100 mg/m^2 melphalan; MDS, myelodysplastic syndrome; MM, multiple myeloma; PACE, cisplatin, adriamycin, cyclophosphamide, etoposide; PACMED, cisplatin, cytarabine, cyclophosphamide, mesna, etoposide, dexamethasone; PEG-G-CSF, pegylated granulocyte colony-stimulating factor; VDT, bortezomib, dexamethasone, thalidomide.

Table 2

(a) Univariate binary logistic regression analysis for variables before mobilization associated with a poor collection (<2.5 × 10^6 CD34 + cells/kg), ordered by increasing *P*-value. (b) Multivariate analysis for all variables before mobilization found associated with a poor collection (<2.5 × 10^6 CD34 + cells/kg) with a $P \leq 0.1$ in univariate analysis (a), ordered by increasing *P*-value

(a)		
Variable	**P-*value***	***OR*[a] *(95% CI)***
Platelet <100 × 10^6/l before mobilization	<0.001	2.43 (1.42–4.16)
G-CSF ± GM-CSF ± Epo	< 0.001	2.77 (1.53–5.01)
Chemotherapy + G-CSF	< 0.001	0.38 (0.22–0.65)
MM-CA[b]	< 0.001	0.08 (0.02–0.32)
Albumin <3.5g/dl	0.003	2.08 (1.26–3.43)
Total therapy participation	0.022	2.14 (1.12–4.06)
Bone marrow cellularity >80%	0.029	0.10 (0.01–0.80)
Hemoglobin < 11 g/dl before mobilization	0.032	1.75 (1.05–2.85)
Female sex	0.047	1.66 (1.00–2.74)
Number of prior aHCTs	0.064	1.41 (0.97–2.05)
Bone marrow cellularity <30%	0.066	1.86 (0.93–3.69)
MDS-CA[b]	NS	NS
MDS-CA present at any time before mobilization	NS	NS
Number of prior relapses	NS	NS
Age > 65 years	NS	NS
Beta-2 microglobulin > 3.5 mg/l	NS	NS
Time from previous aHCT	NS	NS
CD34 count of initial HPC collection per day	NS	NS
Race (Caucasian)	NS	NS
CD34 count of initial HPC collection	NS	NS
Plerixafor	NS	NS
Creatinine >2.0mg/dl	NS	NS
Plasma cell infiltration >60%	NS	NS
WBC <3.5 × 10^6/l before mobilization	NS	NS
CRP > 6 mg/l	NS	NS
Bone marrow morphology consistent with MDS	NS	NS
(b)		
Platelet <100 × 10^6/l before mobilization	0.003	5.34 (2.39–8.01)
G-CSF ± GM-CSF ± Epo	0.030	2.34 (1.42–4.87)
MM-CA[b]	0.042	0.06 (0.02–0.54)
Albumin <3.5g/dl	0.063	2.39 (0.87–15.7)

(a)

Variable	**P-*value***	***OR*[a] *(95% CI)***
Female sex	0.073	1.44 (0.92–5.85)
Bone marrow cellularity <30%	NS	NS
Total Therapy protocol participation	NS	NS
Hemoglobin < 11 g/dl before mobilization	NS	NS
Bone marrow cellularity >80%	NS	NS
Chemotherapy + G-CSF	NS	NS
Number of prior aHCTs	NS	NS

Abbreviations: aHCT, autologous hematopoietic progenitor cell transplant; CA, cytogenetic abnormalities; CI, confidence interval; CRP, C-reactive protein; Epo, erythropoietin; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-monocyte colony-stimulating factor; HPC, hemato-poietic progenitor cell; MDS, myelodysplastic syndrome; MM, multiple myeloma; NS, not significant; OR, odds ratio; WBC, white blood cell.

[a]The OR of a dichotomous variable for a given event represents the ratio of odds of a certain event happening when comparing the two possible outcomes. For continuous variables, the OR represents the same value for an increase of one unit of that variable. An OR > 1 represents a positive correlation of the variable with the effect of interest (higher odds for the event of interest) while an OR<1 represents an adverse one (lower odds for the event of interest).

[b]Within 1-month before mobilization.

Table 3

Characteristics of the infused grafts and time in days to neutrophil and platelet engraftment

Graft group	*Number of infusions*	*CD34 + cells × 10^6/kg infused, median (range)*	*Time to ANC ≥0.5 × 10^9/l, median (range)*[a]	*Time to platelet count ≥20 × 10^6/l, median (range)*[*]	*Time to platelet count ≥50 × 10^6/l, median (range)*[b]
Before aHCT	44	4.95 (2.4–19.2)	10 (8–27)	11 (8–30)	15 (8–60)
After aHCT	86	4.49 (1.2–11.4)	10 (8–79)	12 (8–24)	20 (9–110)
Both	24	4.36 (2.5–17.8)	10 (8–15)	11 (8–30)	16 (10–63)

Abbreviations: aHCT, autologous hematopoietic progenitor cell transplant; ANC, absolute neutrophil count; NS, not significant.

[a] P = NS for all comparisons.

[*] P = NS (compared with either the ‘before’ or ‘both’ group).

[b] $P < 0.001$ compared with the ‘before’ and $P = 0.003$ compared with the ‘after’ group.

Table 4

Variables significantly associated with the development of MDS-CA after a post-aHCT collection by univariate and multivariate binary logistic regression analysis (that is, *P*-value <0.1)

MDS-CA		
Variable	**P-*value***	***OR*[a] *(95% CI)***
Univariate		
MDS-CA present at any time before mobilization	< 0.001	9.70 (3.78–24.8)
Prior MDS-CA[b]	0.009	20.6 (2.06–206)
Hemoglobin <11 g/dl before mobilization	0.016	2.74 (1.20–6.24)
Albumin <3.5g/dl	0.030	2.27 (1.11–3.03)
Poor collection (<2.5 × 10^6 CD34 + cells/kg)	0.035	2.59 (0.97–6.90)
CD34 count of initial HPC collection per day	0.093	0.79 (0.60–1.04)
Multivariate		
MDS-CA present at any time before mobilization	< 0.001	11.6 (3.17–144)
Albumin <3.5g/dl	0.025	3.13 (1.09–8.76)
Clinical MDS/AML		
Univariate		
MDS-CA present at any time before mobilization	0.001	5.88 (2.04–12.34)
Albumin <3.5g/dl	0.013	4.56 (1.30–9.76)
Bone marrow cellularity<30%	0.066	2.77 (0.89–8.33)
Beta-2 microglobulin	0.074	1.01 (0.96–1.03)
CD34 count of initial HPC collection per day	0.086	0.76 (0.58–1.04)
Multivariate		
Albumin <3.5g/dl	0.058	5.18 (0.94–28.4)
MDS-CA present at any time before mobilization	0.076	3.30 (0.87–12.4)

Abbreviations: aHCT, autologous hematopoietic progenitor cell transplant; CA, cytogenetic abnormalities; CI, confidence interval; Epo, erythropoietin; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-monocyte colony-stimulating factor; HPC, hematopoietic progenitor cell; MDS, myelodysplastic syndrome; OR, odds ratio; WBC, white blood cells.

[a]The OR of a dichotomous variable for a given event represents the ratio of odds of a certain event happening when comparing the two possible outcomes. For continuous variables, the OR represents the same value for an increase of one unit of that variable. An OR>1 represents a positive correlation of the variable with the effect of interest (higher odds for the event of interest) while an OR<1 represents an adverse one (lower odds for the event of interest).

[b]Within 1-month before mobilization.