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Increased Efficacy of Stem Cell Chemomobilization with Intermediate-Dose Cytarabine Plus Granulocyte Colony-Stimulating Factor (G-CSF) Compared with G-CSF Alone in Patients with Multiple Myeloma: Results of a Randomized Trial

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Mobilization of hematopoietic stem cells for patients with multiple myeloma (MM) may be done using either steady-state granulocyte colony-stimulating factor (G-CSF) or a combination of chemotherapy with G-CSF. The goal of this randomized, open-label, phase 3 trial was to compare the efficacy of chemomobilization using intermediate-dose cytarabine (ID-AraC) plus G-CSF with G-CSF alone in patients with MM referred for tandem autologous stem cell transplantation (autoSCT). The percentage of patients with stem cell yield of at least 5×10^6 $CD34^+$ cells/kg was the primary endpoint. Ninety patients were enrolled, including 44 assigned to the ID-AraC arm and 46 in the G-CSF arm. The threshold number of $CD34^+$ cells was reached in 43 patients (98%) in the ID-AraC arm and in 32 patients (70%) in the G-CSF arm ($P = .0003$). The median number of collected $CD34^+$ cells was 20.2×10^6 cells/kg in the ID-AraC arm versus 5.9×10^6 cells/kg in the G-CSF arm ($P < .000001$). A single apheresis was sufficient to achieve the required number of harvested $CD34^+$ cells in 37 patients (86%) in the ID-AraC arm and in 13 patients (41%) in the G-CSF arm ($P = .00008$). The times to both neutrophil and platelet recovery after autoSCT were significantly shorter in the patients mobilized with ID-AraC. This study provides the first evidence of the advantage of chemomobilization over G-CSF monotherapy in terms of efficacy. ID-AraC with G-CSF should be the preferred chemomobilization protocol for patients with MM scheduled to undergo tandem autoSCT.

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INTRODUCTION

High-dose therapy with autologous stem cell support (ie, autologous stem cell transplantation [autoSCT]) remains the standard of care for eligible patients with multiple myeloma (MM). Planned tandem autoSCT can also be considered for transplantation candidates and is performed routinely in some centers [1-3]. Currently, peripheral blood is the predominant graft source for autoSCT (99%) [4,5]. Thus, the crucial point in the MM treatment algorithm is allowing for the harvest of an adequate number of stem cells needed for successful and timely hematopoietic recovery. A stem cell dose of 2×10^6 $CD34^+$ cells/kg is considered the absolute lowest threshold for a single autoSCT and should be at least doubled if tandem autoSCT is planned [6-9].

Current first-line mobilization strategies in patients with MM include a steady-state approach with cytokine monotherapy (mostly granulocyte colony-stimulating factor [G-CSF; filgrastim]) or a combination of G-CSF with chemotherapy, most frequently cyclophosphamide (CY), in a so-called "chemomobilization" strategy. The novel CXCR4 agonist plerixafor may be used as a proactive intervention for patients with low $CD34^+$ cell counts in peripheral blood after the aforementioned approaches [6-9]. The efficacy of chemomobilization was compared with steady-state G-CSF in only 1 randomized historical trial in patients with MM and 1 randomized study including patients with lymphoma [10,11]. The addition of CY to G-CSF was found to allow for an increased $CD34^+$ cell yield; however, the proportion of patients achieving the threshold number of $CD34^+$ cells required for transplantation did not differ statistically between the groups. Furthermore, the time to hematopoietic recovery after autoSCT did not differ between the

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groups [10-12]. Thus, the optimal first-line mobilization regimen remains undefined, and local guidelines vary across centers [6-9].

Intermediate-dose cytosine arabinoside (ID-AraC), at a total dose of 1.6 g/m^2 plus G-CSF, has shown very high efficacy as a first- or second-line mobilization regimen in patients with lymphoid malignancies, including MM [13-16]. In a retrospective comparison performed in our center, this strategy was significantly more effective than CY plus G-CSF [14]. This suggests that the type of chemotherapeutic agent added to G-CSF may play a role in mobilization efficacy. Therefore, it seems also reasonable to suppose that the combination of ID-AraC and G-CSF may be more effective than G-CSF alone. The goal of the present study was to verify this hypothesis in a randomized controlled trial.

METHODS

Study Design and Eligibility Criteria

This randomized, open-label, phase 3 trial was conducted in the Department of Bone Marrow Transplantation and Oncohematology, Maria Sklodowska-Curie Institute, Oncology Center, Gliwice Branch, Gliwice, Poland in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, approved by the Institutional Ethics Committee, and registered at www.ClinicalTrials.gov (NCT01908621). All participating patients provided written informed consent.

The inclusion criteria were as follows: (1) diagnosis of MM; (2) age 18 to 65 years; (3) partial or complete response, as assessed by International Myeloma Working Group Guidelines [17] achieved after at least one line of therapy, including 6 or more cycles containing components like thalidomide, lenalidomide, bortezomib, or melphalan; (4) tandem autoSCT planned; (5) World Health Organization performance status 0 to 1; (6) at least a 4-week interval from preceding chemotherapy and a 7-day interval from administration of immunomodulatory drugs; (7) adequate bone marrow function, as demonstrated by a hemoglobin level >8 g/dL, and absolute neutrophil count $>1.5 \times 10^9$/L, and a platelet count $>100 \times 10^9$/L; and (8) adequate renal and hepatic function.

The main exclusion criteria were (1) failure of a previous first-line mobilization regimen; (2) bone marrow plasma cell infiltration >20%; (3) administration of G-CSF within 14 days before the start of study treatment; (4) administration of growth factor other than G-CSF within 4 weeks before the start of study treatment; (5) ongoing or active infection; (6) coexisting neoplasm, other than MM; (7) preceding autoSCT.

Treatment Plan

Patients were alternately assigned to receive mobilization with G-CSF (filgrastim 2×5 μg/kg/day s.c. for up to 7 days) or ID-AraC plus G-CSF (cytosine arabinoside as a 2-hour i.v. infusion at a dose of .4 g/m^2 twice daily every 12 hours on days +1 and +2 (total dose, 1.6 g/m^2), with 2×5 μg/kg filgrastim started on day +5). In the ID-AraC group, complete blood counts were checked every day. The circulating peripheral blood CD34$^+$ cell level was determined on day +5 in the G-CSF group and on the first day of neutrophil recovery from nadir in the ID-AraC group. Apheresis was initiated if the level reached at least 10 cells/μL and was continued daily for up to 3 days or until the target of $\geq 5 \times 10^6$ CD34$^+$ cells/kg was collected.

Apheresis procedures were performed using the Spectra Optia Apheresis System (Terumo BCT, Lakewood, CO) according to the manufacturer's protocol for mononuclear cell collection, processing twice the total blood volume. CD34$^+$ cell counts were determined as described previously [18]. Patients were hospitalized throughout the entire mobilization period owing to regulatory and logistic issues. Tandem autoSCTs were performed after myeloablative therapy (ie, total marrow irradiation at 12 Gy or melphalan 200 mg/m^2) [19].

Efficacy, Safety, and Statistical Methods

The primary study endpoint was the proportion of patients collecting $\geq 5 \times 10^6$ CD34$^+$ cells/kg. Secondary endpoints included (1) number of apheresis days needed to harvest the target number of stem cells; (2) total number of harvested CD34$^+$ cells/kg; (3) peak level of circulating CD34$^+$ cells/μL; (4) proportion of hematologic and nonhematologic complications (according to the Common Terminology Criteria for Adverse Events version 4.0); and (5) time to neutrophil and platelet engraftment, number of blood transfusions, and length of hospital stay after autoSCT.

The size of the study group was based on a power calculation. Given previous single-center experience, it was estimated that 70% of the patients in the G-CSF group and 95% of those in the AraC group would achieve the primary endpoint. With the type I error fixed at $\alpha = .05$ and a power of .8, recruitment of 90 patients was needed to detect the difference.

The 2-sided Mann-Whitney U test was used to evaluate differences between the study groups with regard to quantitative variables, and the χ^2 test was used for qualitative variables. Evaluation of the risk factors for mobilization failure was done using logistic regression. The effect of mobilization on other study endpoints was adjusted for age using multivariate regression.

RESULTS

Patients

Between March 2013 and March 2016, 90 patients were assigned at random to either the G-CSF (n = 46) or ID-AraC (n = 44) study arm. The groups did not differ in terms of MM subtypes, disease stage at diagnosis, number of preceding lines of therapy, frequency of previous radiotherapy, or remission status at mobilization. Patients in the G-CSF arm were older (median age, 60 years [range, 37 to 65 years] for G-CSF the arm and 56 years [range, 33 to 65 years] for the ID-AraC arm; $P = .04$). The most common first-line induction treatment was cyclophosphamide-thalidomide-dexamethasone (82% of all enrolled patients), according to the Polish Myeloma Group recommendations in effect during the study period. Bortezomib-based regimens (mostly bortezomib-doxorubicin-dexamethasone) were used as a second-line treatment. Patient characteristics are summarized in Table 1. A study flow chart is presented in Figure 1.

Efficacy of Mobilization Regimens

A significantly higher proportion of patients in the ID-AraC arm than in the G-CSF arm achieved the primary endpoint of harvesting $\geq 5 \times 10^6$ CD34$^+$ cells/kg (98% [43 of 44] versus 70% [32 of 46]; $P = .0003$). In the single patient in the ID-AraC group who did not collect 5×10^6 CD34$^+$ cells/kg, apheresis had to be interrupted prematurely due to anticoagulant (citrate dextrose solution formula A, ACD-A) cardiac toxicity after processing only one-half the total blood volume. The final stem cell yield was 2.9×10^6 CD34$^+$ cells/kg in this patient. In a multivariate model adjusted for age, the use of G-CSF alone was independently associated with increased risk of mobilization failure (odds ratio, 17.5; 95% confidence interval, 2.1 to 144.9; $P = .007$).

The median number of days of apheresis needed to collect $\geq 5 \times 10^6$ CD34$^+$ cells/kg was 1 (range, 1 to 2) in the ID-AraC group, compared with 2 (range, 1 to 3) in the G-CSF group ($P = .0003$). A single apheresis was sufficient to achieve the primary endpoint threshold number of harvested CD34$^+$ cells in 37 of 43 patients (86%) after ID-AraC but in only 13 of 32 patients (41%) after G-CSF alone ($P = .00008$). The median day of the first apheresis was 13 (range, 12 to 15; SD, .7) after ID-AraC mobilization. The median total CD34$^+$ cell yield was higher in the ID-AraC arm (20.2 [range, 2.9 to 59.4] $\times$x 10^6/kg versus 5.9 [range, 0 to 11] $\times$ 10^6/kg; $P < .000001$) (Figure 2).

The number of CD34$^+$ cells in peripheral blood required to start apheresis was achieved in all patients in the ID-AraC arm and in 44 of 46 patients (96%) in the G-CSF arm ($P = .20$). The median peak number of circulating CD34$^+$ cells was significantly higher in the ID-Ara-C arm (346 cells/μL [range, 11 to 1044 cells/μL] versus 40 cells/μL [range, 1 to 326 cells/μL]; $P < .000001$). Table 2 and Figure 2 summarize the efficacy of studied mobilization regimens.

Toxicity of Mobilization Regimens

All patients in both study arms completed the mobilization period in accordance with the study protocol. One patient in

Table 1
Patient Characteristics

Characteristic	G-CSF Arm	ID-AraC + G-CSF Arm	*P* Value
Number	46	44	
Age, yr, median (range)	60 (37-65)	56 (33-65)	.04
Age >60 yr, n (%)	21 (46)	11 (25)	.04
Sex, male/female, n (%)	26 (57)/20 (43)	27 (61)/17 (39)	.6
Body weight, kg, median (range)	77 (46-105)	80 (57-113)	.7
Paraprotein isotype, n (%)			.4
IgG	24 (52)	26 (59)	
IgA	13 (28)	10 (23)	
Light chain	7 (15)	8 (18)	
Nonsecretory	2 (5)	—	
Stage at initial diagnosis, n (%)			.90
I	5 (11)	4 (9)	
II	14 (30)	14 (32)	
III	27 (59)	26 (59)	
Lines of previous therapy, median (range)	1 (1-5)	1 (1-4)	.50
1 line, n (%)	33 (72)	32 (72)	
2 lines, n (%)	10 (22)	7 (16)	
>2 lines, n (%)	3 (6)	5 (11)	
Cycles of preceding therapy, median (range)	8 (4-19)	8 (4-22)	.60
Previous therapy, n (%)			
Cyclophosphamide	37 (80)	38 (86)	.60
Thalidomide	44 (96)	42 (95)	1.0
Bortezomib	16 (35)	16 (36)	1.0
Doxorubicin	10 (22)	9 (21)	1.0
Lenalidomide	2 (4)	3 (7)	.70
Lenalidomide >4 cycles	1 (2)	2 (5)	.60
Melphalan	1 (2)	1 (2)	1.0
First-line regimen CTD, n (%)	36 (78)	38 (86)	.40
Preceding radiotherapy, n (%)	9 (20)	12 (27)	.40
Disease phase at mobilization, n (%)			.30
Complete remission	7 (15)	3 (7)	
Very good partial remission	16 (35)	18 (41)	
Partial remission	23 (50)	23 (52)	

CTD indicates cyclophosphamide, thalidomide, and dexamethasone.

the ID-AraC group experienced a serious adverse event associated with apheresis (ACD-A cardiac toxicity, as described in Results), leading to premature discontinuation of the collection procedure.

Mobilization with the use of ID-AraC was associated with a 9% incidence of grade 3 neutropenia and a 25% incidence of grade 4 neutropenia. The median duration of neutropenia was 2 days (range, 1 to 3 days) in patients with grade 3 or 4 and 1 day (range, 1 to 3 days) in those with grade 4 (Table 3). In this study arm, 3 patients (7%) experienced grade 2 infection and 1 patient (2%) had a grade 3 infection (Table 4). Specifically, 3 of these 4 patients had an upper respiratory tract infection, and the other patient had a skin infection associated with peripheral venous access catheter use. All infections were managed with the use of topical or systemic (oral route in 2 patients and i.v. in 1 patient) antibiotic or antiviral drugs. The median duration of treatment was 7 days (range, 5 to 14 days). The incidence of infection did not differ statistically between the 2 study arms.

In the ID-AraC group, 27% of patients experienced grade 3 thrombocytopenia, and 48% had grade 4 thrombocytopenia. The median duration of grade 3 or 4 and grade 4 thrombocytopenia was 3 days, (range, 1 to 5 days) and 1 day (range, 1 to 2 days), respectively (Table 3). No bleeding episodes were observed; however, 15 patients (34%) needed platelet transfusion (1 unit in 12 patients and 2 units in 3 patients). The need for RBC transfusions was incidental and comparable in the 2 arms.

During the mobilization period, there were 24 episodes of nonhematologic toxicity in the G-CSF arm and 52 episodes in the ID-AraC arm (Table 4). Most of the episodes were mild to moderate. The incidence of any grade 2 or 3 adverse events was higher in ID-AraC group ($P < .00001$); however, only 3 grade 3 events occurred, all in the ID-AraC arm, and their incidence was not statistically significant compared with G-CSF arm. The most frequent adverse events in the ID-AraC arm

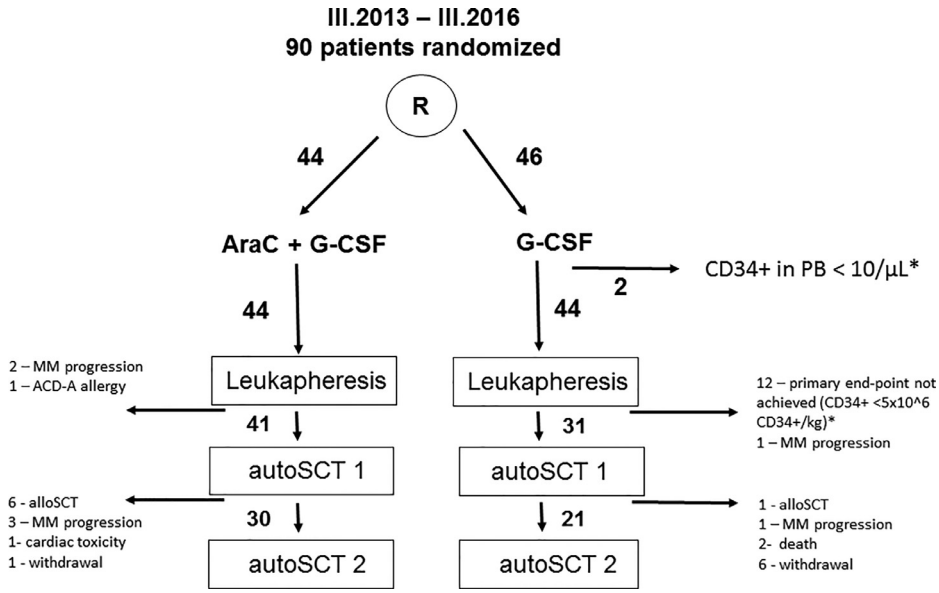
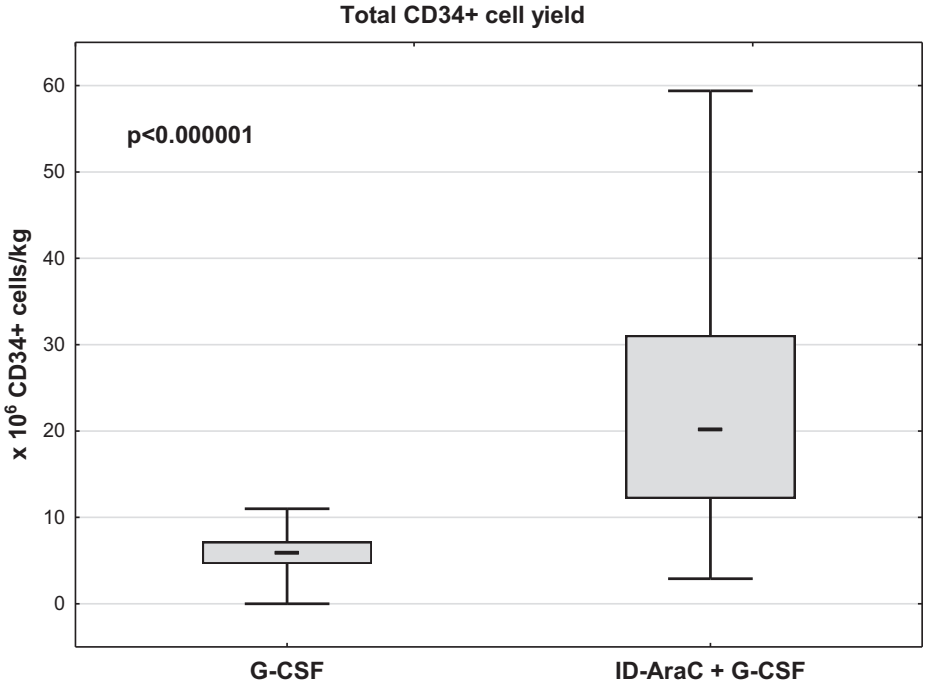


Figure 1. *Among 14 patients who failed to reach target CD34⁺ cell yield after G-CSF mobilization-6 underwent second mobilization using ID-AraC; median CD34⁺ cell yield equaled 14.3 (5.9-24.2) × 10^6 cells/kg; all of them were then treated with tandem autoSCT-4 underwent second mobilization using G-CSF alone; median CD34⁺ cell yield equaled 2.2 (1.0-2.9) × 10^6 cells/kg; in addition to previously harvested peripheral hematopoietic stem cells it allowed to treat them with tandem autoSCT- In 3 patients second mobilization was not performed. The previously harvested peripheral hematopoietic stem cells were used to perform single or double autoSCT despite non-optimal CD34⁺ yield-1 patient was disqualified from transplantation due to acquired plasma coagulation disorder.

(A) Median and range of total CD34$^+$ cell yield (x 10^6/kg) according to the mobilization protocol



(B) Median and range of CD34$^+$ cells (x 10^6/kg) collected on each apheresis day according to the mobilization protocol

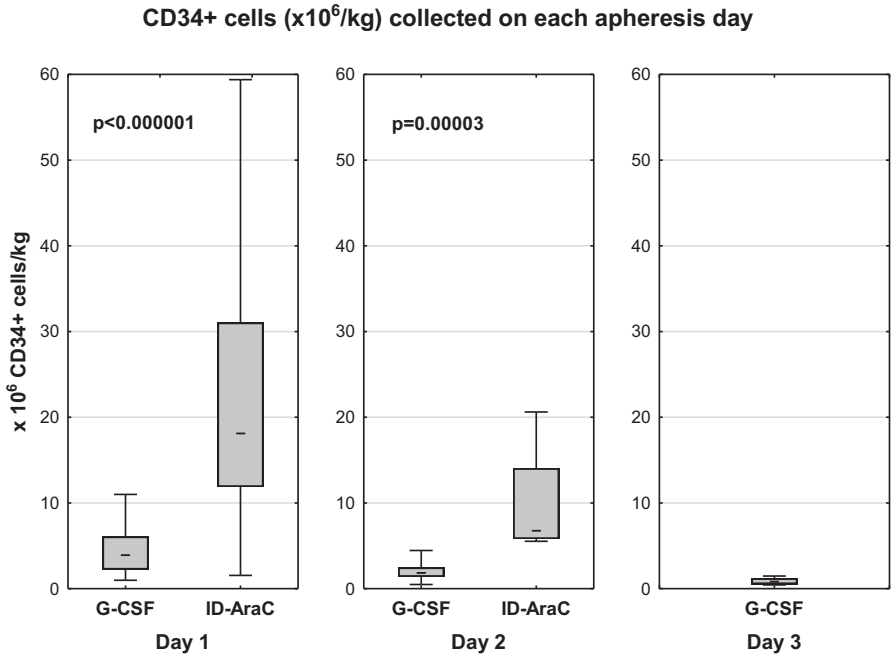


Figure 2. Efficacy of hematopoietic stem cell collection according to the mobilization protocol. (A) Median and range of total CD34$^+$ cell yield ($\times$ 10^6/kg) according to the mobilization protocol. (B) Median and range of CD34$^+$ cells ($\times$ 10^6/kg) collected on each apheresis day according to the mobilization protocol.

were AraC infusion-related nausea and allergic skin reactions, as well as bone pain and hypertension during the period of neutrophil recovery. No cases of grade 4 nonhematologic toxicity were observed.

Hematologic Reconstitution after AutoSCT Procedures

The median number of transplanted CD34$^+$ cells was higher in the ID-AraC arm compared with the G-CSF arm, for both first and second autoSCTs. This was associated

Table 2
Efficacy of Mobilization Regimens

Parameter	G-CSF Arm (n = 46)	ID-Ara-C + G-CSF Arm (n = 44)	*P* Value	*P* Value Adjusted for Age
≥10 $CD34^+$ cells/μL in peripheral blood (required to start apheresis), n (%)	44 (96)	44 (100)	.20	1.0
Peak level of $CD34^+$ cells in peripheral blood/μL, median (range)	40 (1-326)	346 (11-1044)	<.000001	<.000001
Total $CD34^+$ cell yield ($\times 10^6$/kg), median (range)	5.9 (0-11)	20.2 (2.9-59.4)	<.000001	<.000001
$>5 \times 10^6$/kg collected $CD34^+$ cells, n (%)	32 (70)	43 (98)	.0003	.007
Apheresis days to achieve stem cell yield $>5 \times 10^6$/kg, median (range)	2 (1-3)	1 (1-2)	.0003	.000002
Number of apheresis days to achieve stem cell yield $>5 \times 10^6$/kg, n (%)			.00008	—
1	13 (41)	37 (86)		
2	13 (41)	6 (14)		
3	6 (18)	—		
Day of the first apheresis, median (range); mean (SD)	5 (5-7); 5.1 (.30)	13 (12-15); 13.4 (.70)	.000001	.000001
Time of hospitalization in days, median (range)	9 (5-15)	16 (14-21)	.000001	.000001

with a significantly shorter time to neutrophil and platelet engraftment, a lower requirement for platelet transfusions, and a shorter hospital stay after transplantation (Table 5).

DISCUSSION

Nearly 24,000 autoSCTs are performed annually in European Society for Blood and Marrow Transplantation (EBMT) registered centers and 14,000 are performed in the United States, with mobilized peripheral blood the predominant source of hematopoietic stem cells [4,5]. According to an EBMT position statement and American Society for Blood and Marrow Transplantation guidelines, both steady-state and chemotherapy-based mobilization may be considered as a first-line approach in patients with MM, whereas the use of preemptive plerixafor is usually limited to patients at the greatest risk of mobilization failure or as a part of second-line approach [6,7]. However, the optimal mobilization strategy is not clearly indicated, and an established standard does not exist, due in part to the paucity of data from randomized controlled trials.

In the only randomized trial comparing chemomobilization and a steady-state approach in a lymphoma setting published to date, 47 patients with relapsed disease were enrolled. The addition of CY at a dose of 5 g/m^2 to G-CSF allowed for the collection of significantly more $CD34^+$ cells compared with G-CSF as a single agent (median, 7.2×10^6/kg versus 2.5×10^6/kg). However, the number of apheresis sessions required for achieving the established collection target of 1×10^9 total WBCs/kg was similar in the 2 arms (an ~50% success rate in 1 apheresis day). Finally, the times to neutrophil and platelet engraftment after autoSCT also did not differ between the 2 study arms [11]. In the single historical study in an MM patient population, 44 patients were randomized to mobilization with either G-CSF or 6 g/m^2 CY plus G-CSF. The median stem cell yield was significantly higher in the CY group (33.4×10^6/kg versus 5.8×10^6/kg); however, the percentage of patients who achieved the target of 4×10^6/kg considered sufficient for tandem autoSCTs did not differ statistically between the 2 groups (77% in the G-CSF group and 82% in the CY group). Likewise, times to engraftment were comparable in the 2 groups after both transplantation procedures [10]. Recently published results of a randomized comparison of stem cell mobilization between G-CSF and 2 g/m^2 CY plus G-CSF after lenalidomide-based induction therapy in 69 patients with MM showed no statistical difference between the 2 arms in terms of achieving a $CD34^+$ cell yield of at least $\geq 3 \times 10^6$/kg for single autoSCT and $\geq 6 \times 10^6$/kg for tandem autoSCT with 1 or 2 rounds of apheresis [20]. In that study, preemptive use of plerixafor was allowed according to the protocol, which provides bias for a clear comparison between steady-state and chemomobilization.

In our institution, 4 g/m^2 CY plus G-CSF was initially used for the first-line stem cell mobilization. In the event of mobilization failure, we introduced ID-AraC based on the evidence coming from 2 single-center reports, one in patients with chronic lymphocytic leukemia (total dose, 4.8 g/m^2) and the other in subjects with lymphoma (total dose, 1.2 g/m^2) [15,16].

Table 3
Hematologic Toxicity of Mobilization Regimens

Hematologic Adverse Event	G-CSF Arm (n = 46)		ID-AraC + G-CSF Arm (n = 44)	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia, n (%)	-	-	4 (9)	11 (25)
Thrombocytopenia, n (%)	-	-	12 (27)	21 (48)
Interval from mobilization to grade 4 thrombocytopenia, d, median (range)	-		11 (5-12)	
Duration of grade 3 or 4 neutropenia, d, median (range)	-		2 (1-3)	
Duration of grade 4 neutropenia, d, median (range)	-		1 (1-3)	
Interval from mobilization to grade 4 thrombocytopenia, d, median (range)	-		12 (9-14)	
Duration of grade 3 or 4 thrombocytopenia, d, median (range)	-		3 (1-5)	
Duration of grade 4 thrombocytopenia, d, median (range)	-		1 (1-2)	
RBC transfusion required, n (%)	1 (2)		3 (7)	
RBC transfused per patient, units	1		1	
Platelet transfusion required, n (%)	1 (2)		15 (34)	
Platelets transfused per patient, units*	1		1 unit, 12 patients; 2 units, 3 patients	

Toxicity was assessed using Common Terminology Criteria for Adverse Events version 4.0.
* All platelet transfusions were performed using apheresis products, with 1 unit equivalent to 1 transfusion.

Table 4
Nonhematologic Toxicity of Mobilization Regimens

Nonhematologic Adverse Event	G-CSF Arm (n = 46), n (%)			ID-AraC + G-CSF Arm (n = 44), n (%)			*P* Value	
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 2 or 3	Grade 3
Infections	2 (4)	1 (2)	-	-	3 (7)	1 (2)	.20	.30
Skin allergic reaction	-	-	-	5 (11)	2 (5)	-	.10	-
Nausea	-	-	-	3 (7)	4 (9)	1 (2)	.02	.30
Vomiting	-	-	-	3 (7)	-	-	-	-
Hypertension	-	-	-	2 (5)	2 (5)	1 (2)	.07	.30
Bone pain	19 (41)	-	-	12 (27)	10 (23)	-	.0006	-
Constipation	-	-	-	2 (5)	-	-	-	-
Central catheter-related bleeding	-	2 (4)	-	-	-	-	.20	-
Blood bilirubin increased	-	-	-	-	1 (2)	-	.30	-
Any nonhematologic adverse event	21 (45)	3 (6)	-	27 (62)	22 (51)	3 (6)	<.00001	.07

Toxicity was assessed using Common Terminology Criteria for Adverse Events version 4.0.

Table 5
AutoSCT Procedures

Parameter	G-CSF	ID-AraC + G-CSF	*P* Value
Single autoSCT, n	31	41	
Conditioning regimen: HD melphalan/TMI, n (%)	14 (45)/17 (55)	22 (54)/19 (46)	.50
$CD34^+$ dose ($\times 10^6$/kg), median (range)	3.6 (2.1-6.9)	9.4 (2.4-42.2)	<.0000001
ANC >500/μL, median (range)	11 (9-12)	10 (8-11)	.000001
Platelets >20 $\times 10^9$/L, median (range)	17 (14-21)	15 (13-19)	.0003
Platelet transfusions (units), median (range)	1 (0-3)	1 (0-2)	.001
RBC transfusions, n of patients (n of units)	1 (2)	1 (2)	.95
Hospital stay after autoSCT, d, median (range)	14 (12-17)	13 (11-16)	.003
Tandem autoSCT, n	21	30	
Conditioning regimen: HD melphalan/TMI, n(%)	19 (90)/2 (10)	25 (83)/5 (17)	.50
$CD34^+$ dose ($\times 10^6$/kg), median (range)	3.4 (2.7-5.6)	9.6 (2.9-30.1)	<.0000001
ANC >500/μL, median (range)	11 (9-12)	10 (9-11)	.00008
Platelets >20 $\times 10^9$/L, median (range)	17 (15-23)	16 (13-19)	.005
Platelet transfusions, units, median (range)	2 (1-4)	1 (0-3)	.002
RBC transfusion, n of patients (n of units)	2 (1)	1 (2)	.7
Hospital stay after autoSCT, d, median (range)	14 (12-40)	13 (11-23)	.1

The results refer to the observational part of the study.
HD indicates high dose; TMI, total marrow irradiation; ANC, absolute neutrophil count.

In a pilot report, we showed its efficacy when given at a total dose of 1.6 to 2.4 g/m^2 as a second-line salvage mobilization regimen, which was successful in all 13 patients with myeloma and lymphoma [13]. In a subsequent retrospective analysis, we confirmed the greater benefit of 1.6 g/m^2 ID-AraC compared with 4 g/m^2 CY as first-line mobilization in patients with myeloma and lymphoma, among whom a significant proportion (60%) was identified as predicted poor mobilizers [14]. In the ID-AraC group, 95% of patients with MM collected at least 5×10^6 $CD34^+$ cells/kg required for tandem autoSCT, and 97% of patients with lymphoma collected at least 2×10^6 $CD34^+$ cells/kg needed for a single autoSCT, with single apheresis in 92% of cases. Results for the CY group were significantly inferior. The times to both neutrophil and platelet recovery after autoSCT were significantly shorter in the patients mobilized with ID-AraC than in those mobilized with CY [14]. Furthermore, a multicenter analysis from the Polish Lymphoma Research Group (PLRG) demonstrated the superior efficacy of our protocol with 1.6 g/m^2 ID-AraC plus G-CSF over DHAP plus G-CSF chemomobilization in patients with lymphoma [21].

In the present study, we demonstrate for the first time the superiority of ID-Ara-C over G-CSF alone in terms of achieving the primary endpoint of harvesting $\geq 5 \times 10^6$ $CD34^+$ cells/kg. In the ID-Ara-C group, this endpoint was reached by almost all patients (98%), usually with a single apheresis (86%) and at a predictable time of first apheresis day (day 13 with SD <1 day). These results are comparable with our aforementioned retrospective first-line mobilization data [14]. In the G-CSF group, the failure rate was 30%, and only 41% of patients collected the target cell dose with a single apheresis. In previously published retrospective analyses in the MM setting, failure rates were as high as 40% after G-CSF alone [8,10,12,22-24], whereas chemomobilization, mostly with the use of CY, enabled higher stem cell yields but with similar failure rates [8,10,12,22-25]. The advantage of ID-AraC in terms of potency for stem cell mobilization seems to be reflected in the peak number of peripheral blood $CD34^+$ cells, which was almost 9-fold greater than in the G-CSF group. This factor in turn is believed to be the most robust predictor for stem cell collection effectiveness [26-29].

Older age has been identified as a factor that may impair hematopoietic stem cell mobilization or collection [6-9]. In our study cohort, patients in the G-CSF arm were older than those in the ID-AraC arm; nevertheless, in a model adjusted for age, we found that the use of G-CSF alone was independently associated with an increased risk of mobilization failure.

Owing to the significantly higher total stem cell yield in the ID-AraC group, the median number of transplanted $CD34^+$ cells was also higher in tandem autoSCT procedures. This resulted in significantly shorter times to neutrophil and platelet engraftment, as well as a reduced requirement for platelet transfusions. Despite this, however, hospital length of stay was comparable in the 2 arms. Nonetheless, it should be stressed that supportive care, including transfusions and hospital length of stay, refer to the observational part of the study, and thus these variables could have been affected by factors independent of initial randomization.

Our findings regarding the impact of type of mobilization on hematopoietic recovery after autoSCT stand in contrast to the results of the above-referenced randomized studies in which higher stem cell yield obtained after CY-based protocols and higher transplanted $CD34^+$ cell dose did not result in faster engraftment time compared with that seen in the G-CSF group [10-12]. However, several retrospective analyses have shown that an increase in transplanted stem cell dose to >3 to 6 or even 10×10^6/kg is associated with earlier neutrophil and platelet engraftment [24,25,30]. Gertz et al [31] reported on delayed neutrophil and platelet engraftment in patients mobilized with CY plus G-CSF compared with G-CSF alone despite higher $CD34^+$ cell graft content, and suggested transient CY-induced bone marrow microenvironment damage as a cause of slowed engraftment. The discrepancy between those results and our present findings may be explained by distinct mechanisms of drug action, with AraC as an antimetabolite and CY as an alkylating agent. Furthermore, in a clonogenic assay in a retrospective cohort, we observed a trend toward more colonies in AraC-mobilized stem cells compared with CY-mobilized stem cells [14].

Another positive feature of chemomobilization is its potential ability to reduce the myeloma burden. Although this was not a subject of our study, ID-AraC does not appear to provide such a benefit. It also should be noted that such an effect was not shown with the use of CY-based mobilization. Retrospective data did not indicate improvements in overall or progression-free survival with CY plus G-CSF compared with G-CSF alone [32,33].

A disadvantage of chemomobilization compared with G-CSF-only or G-CSF plus plerixafor is greater toxicity, predominantly myelotoxicity [8,12,34,35]. The need for platelet transfusions in 34% of patients may be considered the major disadvantage of an ID-AraC protocol. In contrast, RBC transfusions were required in only 3 patients. In the ID-AraC arm, 34% of patients experienced grade 3 or 4 neutropenia, albeit of very short duration in all cases. This did not translate into the incidence of infections that were incidental and not related to neutropenia. The toxicity issues may be of particular significance in older patients and patients with comorbidities. For patients at high risk of toxicity, the use of G-CSF plus plerixafor seems to be a reasonable alternative. Chemomobilization may be an option in heavily pretreated patients or those who experience plerixafor failure. These characteristics should be individually assessed in patients with MM when choosing the mobilization protocol.

The calculation of costs was not the study endpoint; however, much higher costs may be assumed in the ID-AraC arm. In this study, all patients were hospitalized from the start of mobilization until stem cell collection. This approach was taken owing to logistical and regulatory considerations, not necessarily for medical reasons. An analysis of the toxicity profile suggests that in most cases, ID-AraC mobilization can be run on an outpatient basis. This would require regular blood count controls starting on day 9, the first day on which grade 4 thrombocytopenia was reported in our study. The first leukapheresis can be expected not earlier than day 12. Such an approach likely would allow for substantial cost savings.

In many centers, tandem autoSCT is not a routine practice for patients with MM. For single autoSCT, 2×10^6 $CD34^+$ cells/kg is considered sufficient and can be more readily achieved than our threshold of 5×10^6 $CD34^+$ cells/kg with the use of G-CSF. However, many authors have suggested that higher stem cell yields may be beneficial for autoSCT outcomes, and thus 5×10^6 $CD34^+$ cells/kg is considered optimal for single autoSCT [6-9,24,25,30]. Therefore, our findings also may be useful for centers that do not routinely perform tandem autoSCT.

In conclusion, mobilization with ID-AraC is associated with significantly higher efficacy than mobilization with G-CSF alone. This study provides the first evidence from a prospective randomized trial of the advantages of chemomobilization over G-CSF monotherapy in terms of a higher proportion of patients achieving a sufficient $CD34^+$ cell yield for tandem autoSCT, a higher stem cell procurement rate, and faster hematopoietic recovery after transplantation. In the view of our findings, the use of ID-AraC should be preferred among chemomobilization protocols for patients with MM.

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