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Autologous

Low-Dose Cyclophosphamide versus Intermediate-High-Dose Cyclophosphamide versus Granulocyte Colony-Stimulating Factor Alone for Stem Cell Mobilization in Multiple Myeloma in the Era of Novel Agents: A Multicenter Retrospective Study

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A B S T R A C T

The optimal stem cell (SC) mobilization strategy for patients with multiple myeloma (MM) remains a matter of debate. Possible approaches include low or high doses of cyclophosphamide (Cy), other chemotherapeutic agents, or granulocyte colony-stimulating factor (G-CSF) alone. The scope of the study was to compare low-dose Cy plus G-CSF versus intermediate-high-dose Cy plus G-CSF versus G-CSF alone for SC mobilization in MM, in terms of efficacy and safety. We retrospectively analyzed 422 MM patients undergoing SC mobilization in 6 Italian centers, including 188 patients who received low-dose Cy (LD-Cy group, defined as 2 g/m^2), 163 patients who received intermediate-high-dose Cy (HD-Cy group, defined as $\geq$ 3 g/m^2), and 71 patients who received G-CSF alone (G-CSF group). The median peak of circulating CD34+ cells was 77/μL in the LD-Cy group, 92/μL in the HD-Cy group, and 55/μL in the G-CSF group (P = .0001). The median amount of SCs collected was 9.1 $\times$ 10^6/kg, 9.7 $\times$ 10^6/kg, and 5.6 $\times$ 10^6/kg in the 3 groups, respectively (P = .0001). The rate of mobilization failure (defined as failure to collect $\geq$2 $\times$ 10^6/kg) was 3.7% in the LD-Cy group, 3.4% in the HD-Cy group, and 4.3% in the G-CSF group (P = .9). The target SC dose of at least 4 $\times$ 10^6/kg was reached in 90.4%, 91.1%, and 78.6% of the patients in these 3 groups, respectively (P = .014). The "on demand" use of plerixafor was higher in the G-CSF group (76%) compared with the LD-Cy group (19%) and the HD-Cy group (6%). In multivariate analysis, G-CSF mobilization and previous use of melphalan or radiotherapy were independently associated with failure to collect the target SC dose of $\geq$4 $\times$ 10^6/kg. No impacts of age, blood counts, or previous treatment with lenalidomide, bortezomib, or carfilzomib were observed. Our results suggest that LD-Cy may be considered for successful SC mobilization in patients with MM.

INTRODUCTION

The treatment landscape of multiple myeloma (MM) has changed dramatically over the past decade, thanks to the introduction of novel agents, such as first- and second-generation proteasome inhibitors and immunomodulatory drugs or monoclonal antibodies. Despite these developments, however, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) remains the standard of

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care for young patients with newly diagnosed MM [1-6]. Randomized clinical trials have demonstrated the role of ASCT in the era of novel agents [7,8]. Double (or tandem) ASCT is recommended for high-risk patients and is common practice in Europe [9,10].

The success of the ASCT procedure is strictly related to an adequate hematopoietic stem cell mobilization and harvest. A target of at least 2×10^6/kg CD34+ cells is the minimum cut off for a successful mobilization while the ideal target for 1 ASCT is $>3 \times 10^6$/kg CD34+ cells, and that for 2 ASCTs is $>6 \times 10^6$/kg CD34+ cells [11,12].

The optimal stem cell mobilization strategy remains a matter of debate. Numerous publications have evaluated different mobilization protocols. An International Myeloma Working Group (IMWG) consensus statement [13,14], American Society for Blood and Marrow Transplantation guidelines [15], and a position paper from the European Group for Blood and Marrow Transplantation [16] have been published in recent years.

Currently available mobilization strategies can be divided into 2 groups: chemotherapy-based (mainly with the use of cyclophosphamide [Cy], less frequently with the use of etoposide or cytarabine, plus granulocyte colony-stimulating factor [G-CSF]) and chemotherapy-free (with the use of G-CSF alone or with plerixafor) [11,12]. The preferred protocol varies according to center policy. A Cy-based mobilization strategy is commonly used, with an applied dose varying from 1.5 g/m^2 (low dose, 1.5 to 2 g/m^2) to 4 g/m^2 (intermediate to high dose, 3 to 4 g/m^2). Higher doses are associated with improved stem cell mobilization and collection but also with higher rates of severe neutropenia, infection, and hospitalization. More recently, after the approval of plerixafor (a selective and reversible CXCR4 inhibitor), the chemotherapy-free protocol has been adopted by many centers. It is highly predictable with few side effects and carries no risk of severe neutropenia. However, lower yields have been reported, especially in patients treated with lenalidomide and when a double transplantation is planned.

In Italy, the use of low-dose Cy plus G-CSF is increasingly preferred over high-dose Cy plus G-CSF or cytokine-based mobilization. Low-dose Cy is considered an effective and safe mobilization strategy. It is performed on an outpatient basis and it usually allows the harvest of adequate amounts of peripheral blood stem cells to be used for double ASCT; in fact, most Italian centers have a policy of tandem transplantation. The minimum stem cell collection target is 4×10^6 CD34+ cells/kg, while 6 to 8×10^6 CD34+ cells/kg is the optimal target.

Given the lack of prospective data, here we present the results of a retrospective multicenter analysis comparing low-dose Cy versus intermediate-high-dose Cy versus G-CSF alone as mobilization therapy in patients with MM eligible for ASCT.

METHODS

Patient Population

This retrospective multicenter study compared the use of 3 different mobilizing strategies in patients with MM eligible for ASCT: LD-Cy plus G-CSF versus HD-Cy plus G-CSF versus G-CSF alone.

The analysis included patients with MM eligible for ASCT who underwent at least 1 stem cell mobilization attempt (those with a second mobilization for salvage ASCT were also included) between January 2011 and July 2019, with 1 of the following procedures: Cy 2 g/m^2 plus G-CSF in the LD-Cy group, Cy $\geq$3 g/m^2 plus G-CSF in the HD-Cy group, or G-CSF alone in the G-CSF group. All patients provided written informed consent. The investigators ensured that the study was conducted in compliance with the protocol, adhering to the principles of Good Clinical Practice and in accordance with the principles laid down by the 18th World Medical Assembly (Declaration of Helsinki, 1964 and subsequent amendments). The protocol was approved by the local Ethical Committees of the participating centers.

The main clinical characteristics of the 3 patient groups and the types of induction therapy used before the mobilization phase and ASCT are summarized in Table 1.

Study Treatment

Cy was given at low or high dose (as previously defined) at day 0 of stem cell mobilization. G-CSF was administered s.c. at 5 μg/kg/day starting at day 3 following Cy treatment or 10 μg/kg/day in the G-CSF group. Plerixafor was added to the mobilization protocol according to institutional policy, at a dosage of 240 μg/kg. Peripheral blood CD34+ cells were measured at hematopoietic recovery in the LD-Cy and HD-Cy groups and at day 4 of G-CSF administration in the G-CSF group, and then daily until stem cell collection completion or failure.

A single-platform multicolor flow cytometry analysis was used to enumerate CD34+ cells in either peripheral blood or leukapheresis products. CD34+ cell measurement was performed according to the modified International Society for Hematotherapy and Graft Engineering (ISHAGE) protocol [17,18]. The ISHAGE guidelines have stressed the necessity of using CD45 and CD34 in combination with a sequential Boolean gating strategy for an accurate quantification of CD34+ progenitor cells. Counting beads were used for the absolute counting of CD34-expressing cells. The threshold of peripheral blood CD34+ cells for starting the apheresis procedure was established at 20/μL.

Processed blood volumes were 2.2 to 2.5 in 90% of patients, but as high as 2.8 in the poor mobilizers.

Study Endpoints

The primary study endpoint was a comparison of the 3 mobilization strategies in terms of percentage of patients achieving the minimum stem cell dose for a double ASCT ($\geq 4 \times 10^6$/kg CD34+). The secondary endpoints were defined as follows: (1) percentage of patients who collected the minimum stem cell dose for a single ASCT ($\geq 2 \times 10^6$/kg CD34+); (2) percentage of patients who collected the optimal target dose for a double ASCT ($\geq 8 \times 10^6$/kg CD34+); (3) number of apheresis days required to complete stem cell collection; (4) rate of just-in-time plerixafor administration; (5) incidence of adverse events occurring during mobilization; (6) impact of novel antimyeloma agents on stem cell mobilization; (7) peripheral blood CD34+ maximum peak and peripheral blood CD34+ cell count at first apheresis day; and (8) number of stem cells collected at first apheresis day, at each apheresis day, and in total.

Statistical Analysis

The descriptive statistical analysis was performed separately for the 3 mobilization strategies for all variables considered. In univariate analysis, the relationships between outcomes and the 3 mobilization strategies were evaluated, along with the relationships with clinical and patient history characteristics. The tests used were the Kruskall-Wallis test, Mann-Whitney *U*test, 1-way analysis of variance, and the chi-square test. To obtain odds ratios adjusted for each factor and to verify the presence of possible confounding factors, statistically significant variables in univariate analysis were used to create multivariate models (logistic regression) with each of the 3 different thresholds of minimum stem cell dose considered ($\geq$2, $\geq$4, and $\geq 8 \times 10^6$/kg) as the dependent variables. Statistical significance for all statistical tests was set at $P < .05$. All analyses were performed using the Stata intercooled 14.2 statistical package (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

A total of 422 patients met the inclusion criteria of the study, including 188 patients (44.6%) in the LD-Cy group, 163 (38.7%) in the HD-Cy group, and 71 (16.8%) in the G-CSF group. The median patient age at the time of mobilization was 62 years, with no significant difference among the 3 groups. An induction treatment was always administered before the mobilization attempt, mainly bortezomib-based (66.2%) or lenalidomide-based (9.5%). Thirty-nine patients (9.2%) were treated with carfilzomib before stem cell mobilization. In the entire study population, 86.7% of the patients underwent stem cell mobilization during the first line of MM therapy, whereas 11.4% and 1.9% were mobilized during the second and the third lines of MM therapy, respectively. Few patients were mobilized at relapse. Patient characteristics are summarized in Table 1. Main characteristics did not differ significantly among the 3 study groups. Patients in the G-CSF group were more likely to have received bortezomib-based induction ($P < .001$), whereas carfilzomib-based induction was more common in the LD-Cy group ($P < .001$). Twelve of 71 patients (16.9%) in the G-CSF group had experienced mobilization failure ($P < .001$). Two centers performed only steady-state mobilization, 1 center used only LD-Cy, and all the other centers used all the 3 strategies, according to institutional policies. While in the United States cytokine-based

Table 1
Patient Characteristics

Characteristic	LD-Cy (n = 188)	HD-Cy (n = 163)	G-CSF (n = 71)	*P* Value
Age, yr, median	62	62	62	.9605*
Male sex, %	61	55	44	.039†
International Staging System, %				.779†
I	47	41	54	
II	31	31	28	
III	22	27	18	
Lines of induction therapy, %				.635†
1	89	85	83	
2	10	12	14	
3	1	2	3	
Previous MM therapy, %				
Bortezomib	78	45	87	.000†
Lenalidomide	9	9	13	.587†
≥4 cycles of lenalidomide	94	64	100	.061†
Carfilzomib	16	1	10	<.001†
Previous melphalan therapy, %	3	4	7	.357†
Previous radiotherapy, %	10	14	13	.401†
Previous mobilization failure, %	3	1	17	<.001†
Premobilization status, %				.049†
Complete response	15	14	33	
Very good partial response	40	41	33	
Partial response	39	40	30	
Minor response/stable disease	6	5	4	
Premobilization bone marrow Plasmacells				.019†
<5%	67	46	59	
5-30%	21	36	33	
>30%	11	18	7	
Premobilization parameters, mean				
Hemoglobin, g/dL	12.3	12.4	12	.393‡
Platelets, 10^9/L	213	250	241	.001‡
WBCs, 10^9/L	6.9	5.8	7.4	.083‡
Neutrophils, 10^9/L	2.2	3.5	4.3	.000‡

* Kruskal-Wallis test.
† Chi-square test.
‡ Analysis of variance.

mobilization is considered the standard of care, very few Italian centers adopt a chemotherapy-free approach. This difference is due to physicians' preference and to the concern for higher costs related to the need for plerixafor.

Efficacy of Stem Cell Mobilization

The median peak of circulating CD34+ cells was 77/μL (interquartile range [IQR], 50 to 122/μL) in the LD-Cy group, 92.5/μL (IQR, 51 to 149/μL) in the HD-Cy group, and 55/μL (IQR, 38 to 75/μL) in the G-CSF group (P = .0001). The median number of CD34+ cells collected at the first apheresis day was 4.4 $\times$ 10^6/kg in the LD-Cy group, 7.5 $\times$ 10^6/kg in the HD-Cy group, and 2.7 $\times$ 10^6/kg in the G-CSF group (P< .001). The median peripheral blood CD34+ cell count at first apheresis day was 61/μL in the LD-Cy group, 62/μL in the HD-Cy group, and 45/μL in the G-CSF group (P < .008). A harvest of at least 4 $\times$ 10^6/kg CD34+, the target dose for double ASCT, was reached in 90.4%, 91.1%, and 78.6% of patients in the 3 groups, respectively (P = .014). Plerixafor was used according to a "on demand" strategy; its use was significantly higher in the G-CSF group (76%) compared with the LD-Cy group (19%) and the HD-Cy group (6%).

The total median CD34+ stem cell collection was 9.1 $\times$ 10^6/kg in the LD-Cy group, 9.7 $\times$ 10^6/kg in the HD-Cy group, and 5.6 $\times$ 10^6/kg in the G-CSF group (P = .0001). Stem cell mobilization failure, defined as a collection < 2 $\times$ 10^6/kg, was observed in 3.7%, 3.4%, and 4.3% of patients in the 3 groups, respectively (P = .952). Mobilization and apheresis results are presented in Table 2.

Factors Influencing Stem Cell Mobilization Outcomes

Multivariate analysis results are shown in Table 3. Statistically significant variables in univariate analysis were used to create multivariate models having as dependent variables each of the 3 different thresholds of minimum stem cell dose considered (≥2, ≥4, and ≥8 $\times$ 10^6/kg). Previous treatment with melphalan and previous exposure to radiotherapy were significantly associated with worse stem cell collection. Only 3% of patients in the LD-Cy group, 4% in the HD-Cy group, and 7% in the G-CSF group had been previously exposed to melphalan, but this exposure had an important impact on mobilization outcomes. The 3 treatment groups were equally effective when a cut off of at least 2 $\times$ 10^6/kg was defined. A Cy-based mobilization strategy, regardless of drug dose, was significantly associated with the achievement of higher CD34+ cell counts.

Table 4, Figure 1, and Figure 2 describe factors that had an impact on peripheral blood CD34+ cell maximum peak and total CD34+ cell collection.

Table 2
Mobilization and Apheresis Results

Parameter	LD-Cy (N = 188)	HD-Cy (N = 163)	G-CSF (N = 71)	*P* Value
Mobilization failure, %				
<2 × 10^6 CD34+/kg	3.7	3.4	4.3	.952†
<20/μL peak peripheral blood CD34+	4.3	2.9	4.5	.825†
Total CD34+ cells collected, %				
≥2 × 10^6/kg	96.3	96.6	95.7	.952†
≥4 × 10^6/kg	90.4	91.1	78.6	.014†
≥8 × 10^6/kg	58.5	60.3	20	<.001†
CD34+ cells collected × 10^6/kg, median				
At first apheresis day	4.4	7.5	2.7	<.001*
At second apheresis day	3.9	3.7	2.3	<.001*
At third apheresis day	2.3	2.2	2.1	.519*
Total CD34+ cells collected × 10^6/kg, median	9.1	9.7	5.6	<.001*
Days of apheresis, median	2	1	2	<.001*
Addition of plerixafor, %	19.1	6.1	76.1	<.001*
Peak peripheral blood CD34+ cell count, μL, median	77	92.5	55	<.001*
Peripheral blood CD34+ cell count at first apheresis day, μL, median	61	62	45	.008*

* Kruskal-Wallis test.
† Chi-square test.

Table 3
Multivariate Analysis (Logistic Regression) of Factors Influencing Mobilization Outcomes

Variable	Odds Ratio	95% CI	*P* Value
Total CD34+ cells collected ≥2 × 10^6/kg			
Previous therapy with melphalan	0.06	0.02-0.23	<.001
Previous mobilization failure	0.10	0.02-0.42	.002
Total CD34+ cells collected ≥4 × 10^6/kg			
LD-Cy vs G-CSF	2.39	1.09-5.23	.029
HD-Cy vs G-CSF	2.73	1.17-6.36	.020
Previous therapy with melphalan	0.13	0.04-0.40	<.001
Previous radiotherapy	0.38	0.17-0.85	.018
Total CD34+ cells collected ≥8 × 10^6/kg			
LD-Cy vs G-CSF	5.43	2.78-10.58	<.001
HD-Cy vs G-CSF	6.02	3.02-12	<.001
Previous therapy with melphalan	0.09	0.01-0.75	.026
Previous radiotherapy	0.34	0.17-0.69	.003
Previous therapy with lenalidomide	0.45	0.21-0.96	.038

Table 4
Univariate Analysis of Factors Influencing Peripheral Blood CD34+ Cell Maximum Peak and Total CD34+ Cell Collection

Factor	Value
Peripheral blood CD34+ cell maximum peak	
Previous therapy with melphalan	.0001*
Previous radiotherapy	.0001*
Previous mobilization failure	.0001*
Mobilization using Cy	.0001*
Use of plerixafor	.0001*
Total CD34+ cell collection	
Number of previous lines of myeloma therapy	.0084†
Previous therapy with melphalan	.0001*
Previous radiotherapy	.0001*
Previous mobilization failure	.0001*
Mobilization using Cy	.0001*
Use of plerixafor	.0001*

* Mann-Whitney *U* test.
† Kruskal-Wallis test.

As reported in other studies, previous therapy with lenalidomide had a negative impact on peripheral blood CD34+ cell maximum peak (P = .018), total CD34+ cell harvest (P = .018), and total CD34+ cell collection ≥8 × 10^6/kg (P = .024). In patients treated with carfilzomib, the peripheral blood CD34+ cell maximum peak tended to be lower (P = .011), but the stem cell collection was evenly successful, perhaps owing to the use of plerixafor in 38% of these patients.

The simplified predicted poor mobilizer score was not applicable to our study population, because only very few patients reached 6.5 points [19].

Toxicity

Mobilization protocols were well tolerated. Grade 3-4 neutropenic fever was documented during mobilization in 8 patients in the LD-Cy group and in 2 patients in the HD-Cy group. Importantly, the patients treated with HD-Cy were hospitalized and received adequate antibiotic prophylaxis during severe neutropenia. Fifteen patients overall experienced mild side effects such as nausea, diarrhea, and electrolyte imbalances. The low rate of toxicities precluded comparisons among the 3 groups.

DISCUSSION

In this large retrospective study, we analyzed 422 ASCT-eligible patients with MM who underwent stem cell mobilization with low-dose Cy (LD-Cy group), intermediate-high-dose Cy (HD-Cy group), or G-CSF alone (G-CSF group). In relation to the primary endpoint of the study—a stem cell collection ≥4 × 10^6/kg—a Cy-based mobilization strategy was superior to G-CSF alone. In this study, low-dose Cy proved to be as effective as intermediate-high-dose Cy. Based on these results, a de-escalation of the Cy dose appears reasonable, given that Cy is used solely for stem cell mobilization and not for its antimyeloma activity.

Only 4.52% of patients experienced mobilization failure (3% in the LD-Cy group, 1% in the HD-Cy group, and 17% in the G-CSF group; Table 1). Mobilization failure may occur during the first line of therapy, especially if lenalidomide or carfilzomib are used as induction, or during subsequent lines of therapy when a salvage ASCT is planned. If the patient has already failed a mobilization attempt, the use of plerixafor is generally

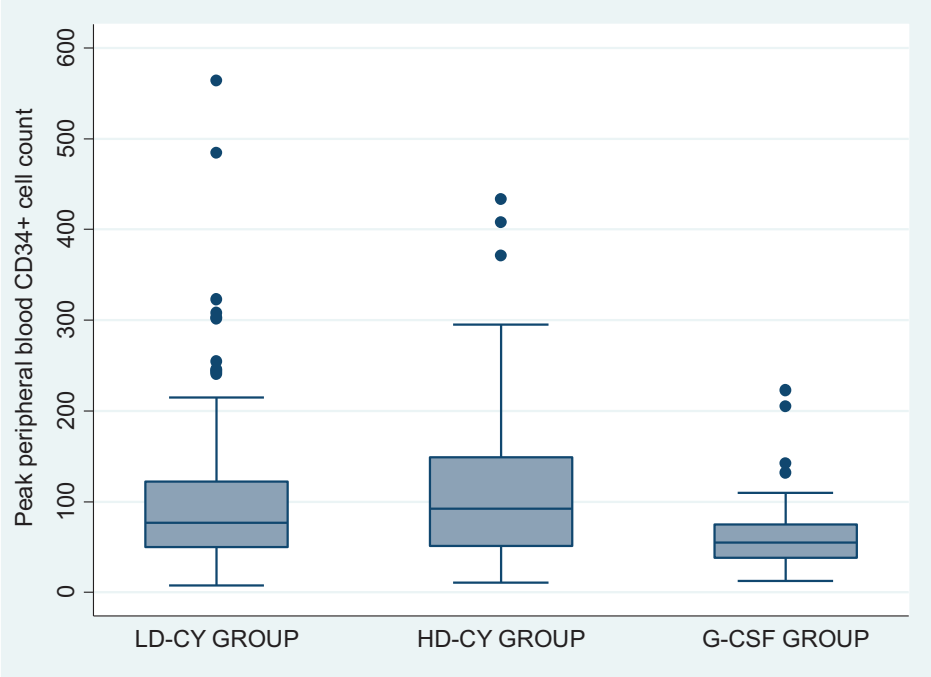

Figure 1. Peripheral blood CD34+ cell maximum peak according to treatment group.

suggested. We can assume that some patients who had experienced a mobilization failure were then mobilized with G-CSF plus plerixafor.

In our series, plerixafor was used in 76% of patients in the G-CSF group and in 19% of patients in the LD-Cy group, with a "on demand" strategy. Unfortunately, we did not perform a pharmacoeconomic analysis; however, both LD-Cy and chemotherapy-free approaches were performed in an outpatient setting, thus avoiding the costs of hospitalization and possibly reducing the incidence of neutropenia-associated infectious episodes [20]. Based on our results, we may suppose that the LD-Cy approach was the most cost-effective, avoiding the costs of hospitalization and plerixafor use.

In multivariate analysis previous treatment with melphalan, previous mobilization failure and previous radiotherapy negatively influenced mobilization outcomes. The use of Cy, regardless of dose, was positively correlated with successful stem cell mobilization and collection. The exposure to lenalidomide was a concern only when the higher stem cell collection target was used ($\geq 8 \times 10^6$/kg).

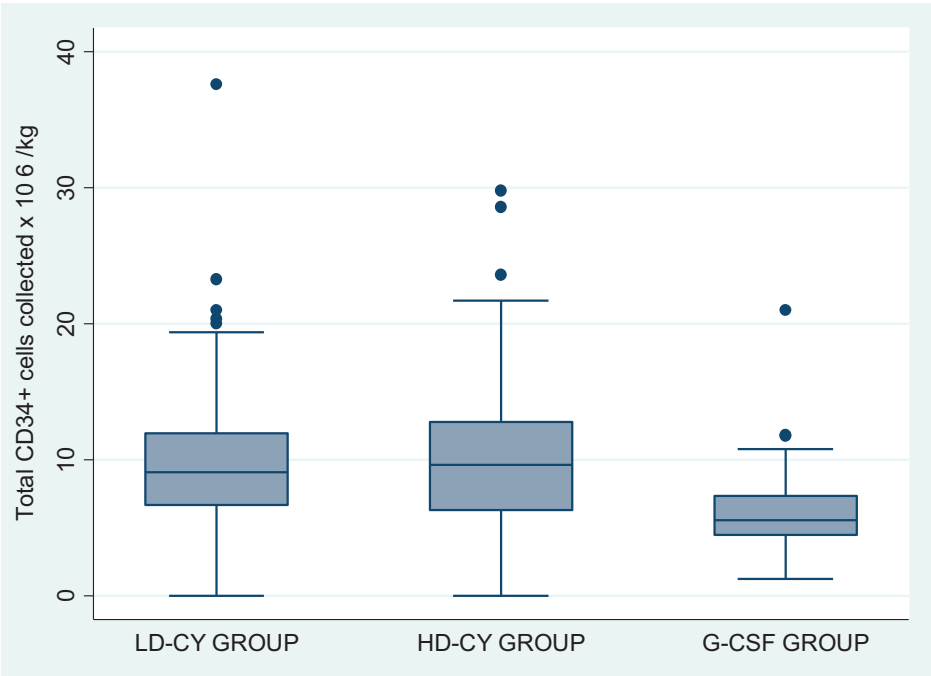

Figure 2. Total CD34+ cells collected according to treatment group.

The optimal stem cell mobilization strategy remains a matter of debate. An International Myeloma Working Group (IMWG) consensus published in 2009 recommended early stem cell mobilization using G-CSF alone after 3 or 4 induction cycles. Cy was recommended for patients treated with more than 4 cycles of lenalidomide, owing to the risk of mobilization failure. The upfront use of plerixafor was not recommended [13,14]. The American Society for Blood and Marrow Transplantation guidelines published in 2014 addressed many questions on stem cell mobilization for autologous and allogeneic SCT in both adult and pediatric populations without a specific focus on MM [15]. In the same year, a position paper from the European Group for Blood and Marrow Transplantation evaluated the pros and cons of steady-state and chemotherapy mobilization [16]. Mobilization with cytokines alone is well tolerated, but their use can be limited by suboptimal peripheral blood CD34+ yields. Adding chemotherapeutic agents to cytokines may increase the amount of stem cells collected; however, the mobilization window is less predictable, and the incidence of severe adverse events is higher. Plerixafor is effective and well tolerated in patients with MM, including poor mobilizers. More recently, 2 reviews have accurately described the status of the art of mobilization in MM [11,12].

Despite these efforts, there is no harmonization in real-world practices, because the mobilization choice depends on local policies and organizations. Chemomobilization remains the standard protocol used by most centers across Europe. This approach is reliable, and many studies have demonstrated a better yield compared with G-CSF alone, especially in patients at risk of poor mobilization (eg, those previous treated with lenalidomide, in case of multiple lines of therapy, those previous exposed to radiotherapy, older age) [21-24]. Toxicity remains a concern, however.

With the introduction of novel agents, Cy is now used solely for its mobilizing effect, and no longer for its antimyeloma activity [25-27]. Doses have been gradually reduced with the aim of minimizing side effects such as febrile neutropenia and the need for hospitalization [28-32]. Winkelmann et al. [28] compared Cy doses of 2.5 g/m^2 and 4 g/m^2 for stem cell mobilization in patients with MM in first remission. A yield of at least 5 $\times$ 10^6/kg CD34+ cells was documented in 83% of patients in both groups, and the rate of mobilization failure did not differ significantly between the groups (14.6% versus 11.3%). The authors concluded that intermediate-dose Cy was as effective as high-dose Cy. Hamadani et al. [29] analyzed 123 patients with MM undergoing stem cell mobilization with LD-Cy (1.5 g/m^2; n= 68) or intermediate dose (ID)-Cy (3 to 4 g/m^2; n = 55) [29]. ID-Cy was significantly superior to LD-Cy in the majority of the mobilization efficacy parameters analyzed, including the number of patients collecting $\geq$2 $\times$ 10^6/kg CD34+ cells on day 1, the number of patients collecting a total of $\geq$5 and $\geq$10 $\times$ 10^6/kg CD34+ cells, and the proportion of patients requiring more than 2 apheresis sessions. The ID-Cy group was associated with a higher incidence of febrile neutropenia (16.3%), hospitalization (20%), and need for red blood cell (34.5%) and platelet (21.8%) transfusions. The choice of the applied Cy dosage level aims to strike a balance between effective peripheral blood stem cell mobilization and a low risk of severe infectious complications. Furthermore, graft cell composition may be significantly influenced by the mobilization protocol, and different studies have shown that chemotherapy-based mobilization has a detrimental effect on immune effectors within the graft, which has been demonstrated to influence patient outcome [33].

The mobilization of autologous peripheral blood stem cells without chemotherapy (chemotherapy-free or steady-state mobilization) is represented by the use of G-CSF alone or with the addition of plerixafor. The combination of G-CSF plus plerixafor was superior to G-CSF alone in terms of achievement of collection targets, lower mobilization failure rates, and fewer apheresis sessions. Despite its effectiveness, however, the cost associated with the upfront use of plerixafor is a major concern [34-45]. Some studies have shown comparable or lower costs with the use of G-CSF plus plerixafor compared with chemomobilization, but others have reported that mobilization without plerixafor is more cost-effective. Plerixafor should be used in poor mobilizers and in patients who have failed the first mobilization attempt. Today, most authors believe that a risk-adapted strategy with the "just in time" addition of plerixafor represents the standard of care for stem cell mobilization.

Our study demonstrates that low-dose Cy plus G-CSF, with the "on demand" addition of plerixafor, is safe and effective for stem cell mobilization in patients with MM. The treatment paradigm and the future scenario of MM are constantly evolving with the introduction of new triplets (bortezomib-lenalidomide-dexamethasone [VRD]; carfilzomib-lenalidomide-dexamethasone [KRD]) and quadruplets (daratumumab-bortezomib-thalidomide-dexamethasone [DARA-VTD]) as induction therapy, the discussed role of double ASCT, the use of maintenance therapy, and the ability to reach and monitor minimal residual disease.

CLINICAL PRACTICE POINTS

Despite the introduction of novel agents, ASCT is still considered the standard of care for patients with newly diagnosed MM aged <70 years. The optimal stem cell mobilization strategy has yet to be defined; possible approaches include Cy at different dose levels and G-CSF alone. We retrospectively analyzed 422 MM patients undergoing stem cell mobilization in 6 Italian centers, including 188 patients who received low-dose Cy (defined as 2 g/m^2; LD-Cy group), 163 who received intermediate-high-dose Cy (defined as $\geq$3 g/m^2; HD-Cy group), and 71 who received G-CSF alone (G-CSF group). An induction treatment was always applied before the mobilization attempt, mainly bortezomib-based (66.2%). The rate of stem cell mobilization failure, defined as collection of <2 $\times$ 10^6/kg, was 3.7% in the LD-Cy group, 3.4% in the HD-Cy group, and 4.3% in the G-CSF group (P = .9). The cut off of at least 4 $\times$ 10^6/kg (target dose for double ASCT), was reached in 90.4%, 91.1%, and 78.6% of patients in the 3 groups, respectively (P = .014). In multivariate analysis, previous treatment with melphalan, previous radiotherapy, and cytokine-only mobilization were independently associated with the failure to collect >4 $\times$ 10^6/kg CD34+ cells. Based on these results, LD-Cy may be considered for successful stem cell mobilization in MM patients who are candidates for ASCT.

MICRO ABSTRACT

We retrospectively analyzed 422 patients with multiple myeloma undergoing stem cell mobilization in 6 Italian centers. The median circulating CD34+ cell peak was 77/μL in the LD-Cy group, 92/μL in the HD-Cy group, and 55/μL in the G-CSF group (P = .0001). The median stem cell collection in the 3 groups was 9.1 $\times$ 10^6/kg, 9.7 $\times$ 10^6/kg, and 5.6 $\times$ 10^6/kg, respectively (P = .0001). The target stem cell dose of at least 4 $\times$ 10^6/kg was reached in 90.4%, 91.1% and 78.6% of patients in the 3 groups, respectively (P = .014). Our results suggest that LD-Cy may be considered for successful stem cell mobilization in patients with MM undergoing ASCT.

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