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Intermediate-dose cytarabine plus G-CSF as mobilization regimen for newly diagnosed multiple myeloma and heavily pre-treated patients with hematological and non-hematological malignancies

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ABSTRACT

Background: Intermediate-dose cytarabine plus G-CSF has recently emerged as safe and effective mobilization regimen for heavily pre-treated patients with lymphoid malignancies. We prospectively tested this regimen in patients referred to our center in order to collect enough stem cells for hematopoietic rescue in autologous transplantation (auto-HSCT).

Study design and methods: cytarabine (1.6 g/m^2) plus G-CSF (outpatient administration) was performed in 81 consecutive patients who underwent auto-HSCT. For analyses purposes patients were divided into Group A, consisted of 48 patients with newly diagnosed multiple myeloma (MM) and Group B with 33 heavily pre-treated patients (13 Hodgkin´s lymphoma, 7 non-Hodgkin´s lymphoma, 7 MM, 4 germ cell tumor, 2 non-promyelocytic acute myeloid leukemia).

Results: In the Group A, circulating CD34+ cells/μL was significantly higher, 90% started stem cell harvest on day 14, 98% collected ≥5.0 × 10^6 CD34+cells/kg and a single apheresis was sufficient in 92% of the cases. In the Group B, 85% started leukapheresis on day 14, 88% collected ≥2.0 × 10^6 CD34+cells/kg which was achieved with a single apheresis in 82% of the cases; a higher proportion of the patients (63.6% versus 33.3%) required platelet transfusions. Both groups exhibited few adverse events and the time to neutrophil and platelet recovery was similar between groups.

Conclusion: Intermediate-dose cytarabine plus G-CSF mobilization is effective even for heavily pre-treated patients. The outpatient administration of G-CSF, the reliable prediction of the day to begin harvesting, the optimal CD34+ cell yield obtained with a single apheresis and the fewer occurrences of adverse events denoted the benefits of this regimen.

1. Introduction

In our center the treatments of greater part of the patients submitted to bone marrow transplantation are entirely dependent on the public budget and most patients are referred from others services after completion of their second or third line of chemotherapy. Hence, pharmacoeconomic aspects, safety or efficacy information are relevant factors influencing the choice of mobilization regimens for autologous hematopoietic stem cell transplantation (auto-HSCT).

Intermediate-dose cytarabine (Ara-C) plus G-CSF has recently emerged as safe and effective mobilization protocol for heavily pre-treated patients with lymphoid malignancies allowing efficient CD34+ cell collection with a limited number of leukapheresis sessions in a larger proportion of the patients [1–4].

Based on these considerations we aimed to assess the efficacy and toxicity of intermediate-dose Ara-C plus G-CSF by examining the stem cell mobilization in newly diagnosed multiple myeloma (MM) and heavily pre-treated patients with hematological and non-hematological malignancies, two groups of patients with different pre-treatment story and distinct from the mobilization perspective.

2. Patients and methods

This study was carried out by the Centro de Hematologia do Vale (CHV). The CHV is a regional hematological center in charge of providing diagnosis, treatment planning and management for oncohematological patients of the PIO XII Hospital in São José dos Campos. This non-teaching hospital has treated patients with hematologic

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Table 1
Patients characteristics.

	Group A	Group B
n	48 (59%)	33 (41%)
Median age (years)[a]	61 (31 – 74)	40 (17 – 69)
Male / female[a]	27(56%) / 21(44%)	17(51%) / 16(49%)
Weight (kg)[a]	72.5 (50 – 121)	71 (51 – 118)
MM	48 (100%)	7 (21.2%)
CR	9	0
VGPR	12	0
PR	27	7
HL	0	13 (39.4%)
Relapse, CR	0	5
Relapse, PR	0	6
Primary resistence, PR	0	2
NHL	0	7 (21.2%)
Relapse, CR	0	2
Relapse, PR	0	4
Primary resistence, PR	0	1
GCT	0	4 (12.1%)
AML	0	2 (6.1%)
Months from diagnosis to mobilization[**]	7 (5 – 9)	13 (11 – 47)
Preceding 1 chemotherapy regimen[**]	48 (100%)	0
Preceding 2 chemotherapy regimens[**]	0	16 (49%)
Preceding > 2 chemotherapy regimens[**]	0	17 (51%)
Preceding radiotherapy[**]	3 (6%)	7 (21.2%)
Previous auto-HSCT[**,b]	0	8 (24.2%)

Abbreviations: CR = complete response, VGPR = very good partial response, PR = partial response. Data were expressed as median (min-max) or absolute number (%).

[a] Data not different at 0.05 level.

[b] (relapsed patients after first auto-HSCT without cryopreserved PBSC for a second transplant, 7 MM and 1 GCT).

** $P < 0.01$.

malignancies since 1999 and it is the referral center for stem cell transplants for patients from the Regional Health Division XVII, composed of 39 municipalities in the Vale do Paraíba.

From January 2016 to February 2018, 81 consecutive patients who underwent high-dose chemotherapy followed by autologous stem cell rescue were included in this prospective study. For analyses purposes patients were divided into two groups according to the CD34+ threshold required for one or two auto-HSCT; Group A consisted of with newly diagnosed multiple myeloma (MM) and Group B consisted of heavily pre-treated patients with Hodgkin´s lymphoma (HL), non-Hodgkin´s lymphoma (NHL), germ cell tumor (GCT), non-promyelocytic acute myelogenous leukemia (AML) and relapsed MM after auto-HSCT (Table 1).

Patients with newly diagnosed MM were treated with an induction therapy consisting of cyclophosphamide and dexamethasone (CD), thalidomide combined with cyclophosphamide (Cy) and dexamethasone (CyTD), VAD (vincristine, doxorubicin and dexamethasone) and Cy, bortezomib and dexamethasone (CyBorD). HL and NHL patients were treated with DHAP, ESHAP or ICE salvage chemotherapy. Remission induction with Ara-C plus daunoblastin was administered in AML patients and ifosfamide-based regimens in patients with GCT. Dexamethasone, Cy, etoposide, and cisplatin (DCEP) was the salvage regimen for relapsed MM patients after first auto-HSCT. Only patients with at least partial response of their disease and proven chemosensitivity were accepted for auto-HSCT in our service. Patients who did not achieve a remission status were not eligible. All patients gave written informed consent.

Peripheral blood stem cells (PBSC) were mobilized according to the protocol described in Table 2. Patients were hospitalized on the first day and discharged from hospital on day 3. Antimicrobial prophylaxis was not used. From day 6 to day 13 G-CSF was daily administered in the ambulatory care setting. On day 13 patients were re-hospitalized for the following additional procedures: venous blood sample collection for blood cell counts and enumeration of circulating CD34+ cells, transfusions when indicated and central venous catheter insertion. Platelets transfusions were indicated when the platelet level dropped below 20×10^9/L or 30×10^9/L for the introduction of the central venous line. Packed red blood cells (RBC) were administered to maintain hemoglobin level around 10 g/dL. On day 14, patients who met the circulating CD34+ cells criteria started leukapheresis in a limited number of two sessions. During the entire period of mobilization patients were evaluated for hematologic and non-hematologic adverse reactions. The toxicity of the mobilization protocol was assessed using Common Terminology Criteria for adverse events [5].

Table 2
Mobilization protocol and collection of PBSC.

Days	Procedures
1 to 2	Ara-C administered as 2 h i.v. infusion at a dose of 0.4 g/m^2 twice daily
3	Discharge from hospital
4 to 5	–
6 to 14	G-CSF administered as s.c. infusion at a dose of 12 μg/Kg
14	Stem cell harvest

The enumeration of CD34+ cells was performed when neutrophils > 1.0×10^9/L; if this level was not achieved on day 13, G-CSF administration was daily continued until the neutrophil count exceeded 1.0×10^9/L. A minimum threshold of 10 circulating CD34+ cells per microliter (μL) was required for leukapheresis; if this level was not achieved on day 13, G-CSF administration was daily continued until the circulating CD34+ count exceeded the respective threshold. The CD34+ cells were determined according to the International Society of Hematotherapy and Graft Engineering (ISHAGE) guidelines as previous described [6].

PBSC were collected with the intermittent-flow blood cell separator Haemonetics MCS + 9000E (Haemonetics Corporation, Massachusetts, USA) according to the manufacturers´ protocols for mononuclear cell harvesting. The target CD34+ cell yield was 5.0×10^6 CD34+/kg for Group A (enough CD34+ cells planned for a second auto-HSCT). For Group B the endpoint of the protocol was the successful mobilization of a target CD34+ cell yield of 2.0×10^6 CD34+/kg (planned for a single auto-HSCT).

PBSC were cryopreserved using a mixture of 10% dimethylsulfoxide (DMSO), 6% hydroxyethyl starch (HES) and 4% human serum albumin (HAS) as cryoprotectant without controlled-rate freezing at −84 °C.

Statistical analyses were evaluated in a nonparametric non-paired fashion with the Mann-Whitney U test; categorical variables were compared with the Fischer´s exact test. P values of less than 0.05 were considered to indicate statistical significance. The data analyses were performed with the GraphPad Prism 6 software.

3. Results

As demonstrated in Table 1, Group A showed higher median age and 27 out of 48 patients (56%) were categorized as partial remission. The majority of the Group B was exposed to more than two lines of preceding chemotherapy including radiotherapy or prior auto-HSCT. Exposure to radiotherapy ($P = 0.007$) and greater than two prior chemotherapy regimens ($P = 0.005$) were found to be associated with lower CD34+ yield in Group B.

Circulating CD34+ cells/μL was significantly higher in Group A compared with Group B [median 146 (range, 9–778) versus 32 (range, 3–738), $P < 0.0001$, respectively]. All patients reached ≥10 CD34+ cells/μL but the proportion of patients who reached at least 10 CD34+ cells/μL and started stem cell harvest on day 14 was also higher in group A. Overall, 71 out of 81 patients (88%) proceeded to leukapheresis on day 14 of the protocol (Table 3).

Table 3
Circulating CD34+ cells and stem cell harvest between day 14 and 18.

	Days of the mobilization protocol					
	13	14	15	16	17	18
Neutrophil ≥1 × 10^9/L[a]						
Group A	48 (100%)					
Group B	30 (91%)	2 (6%)		1 (3%)		
Circulating CD34+ ≥10/μL[a]						
Group A	43 (90%)		4 (8%)	1 (2%)		
Group B	28 (85%)		2 (6%)		3 (9%)	
First leukapheresis[a]						
Group A		43 (90%)		4 (8%)	1 (2%)	
Group B		28 (85%)		2 (6%)		3 (9%)

Data were expressed as absolute number and (%) of the patients.
[a] Data not different at 0.05 level.

Table 4
First harvest parameters and results.

	Group A	Group B
Pre-leukapheresis		
Hemoglobin (g/dL)[a]	10.3 (6.3 – 13.6)	9.5 (6.2 – 13.1)
WBC (x10^9/L)[a]	9.1 (1.7 – 36.4)	8.2 (0.2 – 49.3)
Platelets (x10^9/L)[**]	42.0 (7.0 – 113)	24.0 (2.0 – 204)
Leukapheresis		
Volume processed (mL)	7554 (4338 – 10,180)	7267 (6096 – 9633)
ACD-A (mL)[a]	781 (525 – 1026)	745 (639 – 983)
Time (minutes)[a]	260 (185 – 340)	252 (226 -340)
Leukapheresis product		
Volume (mL)[a]	156 (119 – 180)	160 (125 – 185)
WBC (x10^6/mL)[a]	343.5 (114.0 – 711.2)	334.2 (83.2 – 773.9)
Cell viability (%)[a]	92 (82 – 99)	93 (83 – 99)
CD34+ (x10^6/Kg)[**]	12.7 (1 – 45.7)	3.8 (0.8 – 22.7)

Abbreviations: WBC = white blood cells, ACD-A = anticoagulant citrate dextrose solution. Data were expressed as median (min-max).
[a] Data not different at 0.05 level.
** P < 0.01.

Table 5
Rates of mobilization efficiency.

Group A	
Patients with ≥5 × 10^6/kg CD34% cells after the first leukapheresis	44 (92%)
Patients with ≥5 × 10^6/kg CD34% cells after two leukapheresis	47 (98%)
Patients with > 2 and < 5 × 10^6/kg CD34% cells after two leukapheresis	1 (2%)
Group B	
Patients with ≥2 × 10^6/kg CD34% cells after the first leukapheresis	27 (82%)
Patients with ≥2 × 10^6/kg CD34% cells after two leukapheresis	29 (88%)
Patients with > 1 and < 2 × 10^6/kg CD34% cells after two leukapheresis[*,c]	4 (12%)

Data were expressed as absolute number and (%) of the patients.
[c] (1 patient with HL, 1 NHL, 1 AML and 1 MM).
* P < 0.05.

The CD34+ cell yield was significantly higher in Group A (Table 4). In Group B the number of CD34+ cells (×10^6/kg) according to diagnosis were as follows: HL 5.5 (range 1.1–22.7), NHL 4.2 (range 1.2–6.4), GCT 5.9 (range 3.4–8.3), AML 1.5 (range 0.9–2.7) and relapsed MM after auto-HSCT 2.0 (range 0.8–4.5). A single apheresis was sufficient to collect adequate numbers of CD34+ cells in 92% patients in the Group A compared to 82% in the Group B. Both groups showed lower proportion of patients with mobilization failures (Table 5).

Days 1 and 2 of the mobilization protocol were uneventful; from days 6–13 patients did not require hospitalization nor showed persistent or substantial disabilities or had important medical consequences.

Table 6
Adverse events observed during the mobilization protocol.

	Group A	Group B
Hematologic		
Neutropenia		
Grade 2[a]	1 (2%)	3 (9%)
Grade 3[a]	0	0
Grade 4[a]	0	3 (9%)
Thrombocytopenia		
Grade 2[a]	22 (45.8%)	11 (33.3%)
Grade 3[**]	6 (12.5%)	10 (30.3%)
Grade 4[**]	1 (2.1%)	4 (12.1%)
Transfusion		
Packed RBC[a]	15 (31.3%)	9 (27.2%)
Platelet[**]	16 (33.3%)	21 (63.6%)
Non-hematologic		
Bone pain[a]	2 (4.1%)	1 (3%)
Weakness[a]	1 (2%)	2 (6%)
Allergy[a]	1 (2%)	0
Diarrhea[a]	0	1 (3%)
Dyspepsia[a]	0	2 (6%)
Elevated creatinine[a,d]	1 (2%)	1 (3%)

Data were expressed as absolute number and (%) of the patients.
[a] Data not different at 0.05 level.
[d] creatinine values ranging from 1.3 to 1.5 mg/dL.
** P < 0.01.

Two patients were hospitalized during the whole mobilization period due to the distance from the patient´s place of living to the hospital. Patients from both groups did not experience febrile neutropenia. The hematologic adverse reactions were comparable between the groups except for more frequent Grade 3 or 4 thrombocytopenia found in Group B and consequently a higher proportion of patients who required platelet transfusions (Table 6).

All patients proceeded to auto-HSCT directly after mobilization and received standard supportive treatments including antibiotics and blood component transfusion; G-CSF 300 μg per day was administered from day 3 after auto-HSCT until engraftment. No patient experienced graft failure. The median time to neutrophil > 0.5 × 10^9/L was 11 days (range, 9–12) in Group A compared to 12 days (range, 9–14) in group B (data not different at 0.05 level). As well, the time to platelets > 20 × 10^9/L was similar in both groups [Group A, median 12 days (range, 10–15), Group B, median 14 days (range, 10–18)]. Days to neutrophil or platelet recovery from patients who received < 2 × 10^6/Kg CD34+ were similar with those observed in the entire sample of the Group B.

4. Discussion

This is a single institutional study of PBSC mobilization and collection in patients with lymphoid, myeloid and non-hematological malignancies using intermediate-dose Ara-C plus G-CSF as mobilizing regimen. Based on the fact that Groups A and B are highly heterogeneous from the mobilization perspective we believe that the sample size for this study was enough to draw meaningful suggestions.

Stem cells can be mobilized into the peripheral blood with various chemotherapy regimens and growth factors with differ according to efficiency, toxicity and costs. The main goal is to prevent mobilization failure. Giralt et al. [7] analyzed 38 studies with different mobilization regimens in various diagnosis and reported that the failure rates were high as 40%. Some characteristics of the patients including age, sex, diagnosis, stage of the disease (complete or partial remission), previously administered radio or chemotherapy, time elapsed from diagnosis to mobilization and mobilization strategies are always considered as possibly predictive of failed mobilization [8–10]. Accordingly, CD34+ cells/kg was significantly higher in newly diagnosed MM patients. In addition, exposure to radiotherapy and greater than two prior chemotherapy regimens but not diagnosis were found to be associated

with lower yield in Group B. In both groups age, sex and time between diagnosis and mobilization were not associated with CD34+ cell yield.

The most common stand-alone regimens for stem cell mobilization include Cy at a range of doses. Higher doses of Cy (3–7 g/m^2) are associated with higher cells yields, but also may result in more toxicity and higher costs. Giebel et al. [2] compared intermediate dose Ara-C with Cy at a dose of 4.0 g/m^2 and demonstrated that the mobilization results for the Cy group were significantly inferior. The number of collected CD34+ cells was significantly higher for patients mobilized with Ara-C than Cy and a single leukapheresis was sufficient to collect the desired CD34+ cells threshold in 91% patients in Ara-C group compared to 24% in the Cy group. Moreover, in patients with MM (n = 39, 26% partial remission) Ara-C was associated with higher peak number of circulating CD34+ cells (136/μL) and 95% patients collected at least 5.0 × 10^6 CD34+ cells/kg; among 31 patients with lymphomas (Hodgkin and non-Hodgkin) the peak number of circulating CD34+ cells was 78/μL and 97% collected > 2 × 10^6/Kg CD34+ cells. Overall, 35% required platelet transfusions and 26 out of 28 patients (93%) with high risk of mobilization failure collected adequate number of CD34+ cells. Gojo et al. [11] studied 77 MM patients mobilized with either Cy (4.5 g/m^2, n = 28) alone or associated with etoposide 2 g/m^2 (n = 49) and described a median of 22.9 × 10^6 CD34+ cells/Kg collected on the first leukapheresis in 92% of patients. However, in both arms the proportion of patients who required hospitalization for treatment of neutropenic fever was unacceptable. Additionally, in a previous study we tested the combination of Cy (1.5 g/m^2) plus G-CSF in patients with MM and NHL; the proportion of patients with higher CD34+ cell yield after two leukapheresis was 73% and 71% in MM and NHL, respectively. Patients did not require hospitalization nor had important medical consequences. [10] Recently, in a pilot trial Heizmann et al. [12] evaluated stem cell mobilization with vinorelbine (35 mg/m^2) and G-CSF in patients with lymphoma and showed that stem cell collection was successfully performed in 43 patients (96%); for 28 patients (62%) a sufficient stem cell yield was reached with one apheresis. Samaras et al. [13] assessed the efficacy of vinorelbine (35 mg/m^2) plus G-CSF in 221 MM patients and showed that in the great majority (77%), the predefined amount of 4.0 × 10^6 CD34$^+$ cells/kg was collected with one leukapheresis.

With regard to some parameters such as the peak level of CD34+ cell in peripheral blood, the CD34+ cell yields, the percent of single apheresis and the proportion of patients who required transfusions, data obtained from Group A were similar with those previously demonstrated by Giebel et al. [2] and apparently superior to other above-cited studies [10–13] in terms of efficacy or toxicity. Interestingly, the majority in Group A was classified as partial remission and it is important to shed some light on this question. Around 80% of the patients referred to our service came from the Brazilian National Health System (named SUS). Unfortunately, there is no currently government approval for the use of lenalidomide and proteasome inhibitors for MM and chemotherapy regimens such as CD, VAD or CyTD which have led to modest response rates, are still used today in the SUS care setting. By way of illustration, Vigolo et al. [14] compared the response rates obtained with CyTD and CyBorD as induction therapy for Brazilian MM patients and found complete response rates of 7.1% and 45.5% patients, respectively. Taken altogether, it is reasonable to consider that these aspects reflected in the proportion of patients with partial response in Group A but this specific characteristic did not impair the ability to mobilize PBSC.

In comparison with Giebel et al. [2] Group B showed differences such as the lower number of circulating CD34+ cells, the lower percent of patients who collected adequate number of CD34+ cells and the higher number of patients who required platelet transfusions. The possible explanations are based on Group B characteristics; although consisted of different diagnosis, all patients were exposed to at least two lines of preceding chemotherapy including radiotherapy or prior auto-HSCT and most of them met the criteria for poor mobilizer proposed by Olivieri et al. [15]. These patients were essentially not expected to mobilize well even when a low target cell dose of 2.0 × 10^6 CD34+/kg is selected. It is possible that in patients treated extensively for their malignancies the failures likely represent accumulated marrow toxicity. However, even under this adverse scenario adequate number of CD34+ cells were achieved in 88% of the patients and 82% proceeded to a single apheresis. These findings were similar with those previously described [10–13] and also supported by subsequent work by Giebel et al. [4] in which the authors enrolled patients with lymphoma who had received at least 2 lines of chemotherapy and compared the efficacy between intermediate-dose Ara-C plus G-CSF and DHAP plus G-CSF for stem cell mobilization; the Ara-C arm was associated with a higher efficacy and a single apheresis was sufficient to achieve the threshold number of CD34+ cells in 82% of the cases. In addition, Calderon-Cabrera et al. [3] reported on 33 lymphoma patients who had three lines of previous chemotherapy and at least one prior mobilization failure and received intermediate-dose cytarabine as mobilization regimen; overall, the mean number of apheresis procedures was 2 and 97% reached the target CD34+ cell dose of 2.0 × 10^6/Kg.

Importantly, Giebel et al. [2] also reported that 84% of the patients started leukapheresis between day 13 and 15, most frequently on day 14. Based on this information, we planned a mobilization protocol including stem cell harvest on day 14; as demonstrated, 43 patients (90%) in Group A and 28 (85%) in Group B started leukapheresis on day 14. Our data confirm that this protocol allows a more reliable prediction of the day to begin harvesting of PBSC minimizing costs and discomfort to the donors caused by the leukapheresis procedure.

All patients from both groups successfully engrafted following conditioning chemotherapy. Despite the lower number of CD34+ cells transplanted in four patients from Group B there were no significant differences with regard to time needed for hematologic reconstitution.

In conclusion, our data also suggest that intermediate-dose cytarabine associated with G-CSF is a feasible and effective mobilization regimen even for patients considered poor mobilizers. Furthermore, the capability of an outpatient administration of G-CSF, the possibility to make more reliable prediction of the day to begin harvesting of PBSC, the optimal CD34+ cell yield obtained with a single apheresis, the minimal risk of febrile neutropenia and the fewer occurrences of hematologic and non-hematologic adverse events also denoted the benefits of this scheme. Despite our data compared agreeably with other regimens in terms of the rates of harvesting efficiency, it should be stressed that the protocol presented in this study may be not the best mobilization regimen for all patients. Finally, considering the heterogeneity among the health facilities, particularly in low-income countries, we believe that our data would add practical guidance to centers that are conducting mobilization of PBSC.

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