

Mobilization of hematopoietic progenitor cells with granulocyte colony stimulating factors for autologous transplant in hematologic malignancies: a single center experience

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Background: In 2006 the Hematology Service of Hospital Maciel published its experience with peripheral blood progenitor cell harvesting for autologous stem cell transplantation using Filgen JP (Clausen Filgrastim). After mobilization with a mean filgrastim dose of 78 mcg/Kg, 4.7×10^6 CD34⁺ cells/Kg were obtained by apheresis. Age above 50, multiple myeloma as underlying disease and a malignancy that was not in remission were identified as frequent characteristics among patients showing complex mobilization.

Objective: The aim of this study was to compare stem cell mobilization using different brands of filgrastim.

Methods: One hundred and fifty-seven mobilizations performed between 1997 and 2006 were analyzed. This retrospective analysis comparative two groups of patients: those mobilized with different brands of filgrastim (Group A) and those who received Filgen JP (Clausen Filgrastim) as mobilizing agent (Group B). A cluster analysis technique was used to identify four clusters of individuals with different behaviors differentiated by age, total dose of filgrastim required, number of apheresis and harvested CD34⁺ cells.

Results: The mean total dose of filgrastim administered was 105 mcg/Kg, the median number of apheresis was 2 procedures and the mean number of harvested stem cells was 4.98×10^6 CD34⁺ cells/Kg. No significant differences were observed between Groups A and B regarding the number of apheresis, harvested CD34⁺ cells and number of mobilization failures, however the total dose of filgrastim was significantly lower in Group B.

Conclusions: Among other factors, the origin of the cytokine used as mobilizing agent is an element to be considered when evaluating CD34⁺ cell mobilization results.

Keywords: Filgrastim; Hematopoietic stem cell mobilization; Blood component removal

Introduction

Background

Stimulation using granulocyte growth factors associated or not to chemotherapy, is broadly used as a method in the mobilization of hematopoietic progenitor cells (HPC) from bone marrow or peripheral blood. This technique has been widely used for over two decades since the papers of Haas and Siena et al.⁽¹⁻⁴⁾ Hematopoietic progenitor cells express the CD34 molecule on their surface, allowing their identification and quantification by flow cytometry in peripheral blood, thus determining the optimal time for their harvest by leukapheresis.

In the setting of an autologous stem cell transplantation (ASCT) program, stem cell mobilization and harvest must be reproducible. The goal is to obtain the required number of cells to ensure bone marrow engraftment, with the lowest growth factor dose and minimizing the number of leukapheresis.

The success of mobilization not only depends on the characteristics and growth factor dose, but also on patient characteristics (age and personal background) as well as on the underlying disorder (disease extension, chemotherapy and/or radiotherapy burden and intensity).

Different granulocyte growth factors have been used as mobilizing agents of CD34⁺ cells, such as filgrastim, molgramostim and lenograstim. Filgrastim is the most used agent for this purpose.

This study evaluated the results obtained with Filgen JP (Clausen Filgrastim) as the mobilizing agent.⁽⁵⁾

Disclosures:

Drs. Gabús, Borelli, Ferrando and Bódega and Alvarez have no conflict of interests. Drs. Citrín and Olivera Jimenez are both employees of the Clausen Laboratories S.A. of Montevideo, Uruguay

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Institutional setting

The Hospital Maciel [Administración de Servicios de Salud del Estado, A.S.S.E. (Administration of State Health Services), Montevideo, Uruguay] is a national reference general public hospital. Its Hematology Service was inaugurated in June 1994 and the stem cell transplantation (SCT) program started in February 1996. The Hematology Service of the Hospital Maciel is the only public SCT centre (both allogeneic and autologous) for adults in Uruguay.

Between February 1995 and December 2010, 333 (myeloablative and non-myeloablative, related and unrelated) SCT were performed in 317 patients. Eighty percent of transplants were autologous and 20% corresponded to different modalities of allogeneic SCT. Patients submitted to SCT were aged between 15 and 67 years old. Fifty-eight percent of patients were from the National Health Service and 42% from the private system ["Instituciones de Asistencia Médica Colectivizada" (IAMC)].

Hematopoietic progenitor cell harvesting

The sources of HPCs used for ASCT in our service were peripheral blood (91.8%), bone marrow and peripheral blood (7.6%) and bone marrow (0.6%). Peripheral blood progenitor cells (PBPC) were harvested by leukapheresis after mobilization with filgrastim or chemotherapy plus filgrastim.

There is a close relation between the infused CD34⁺ cell number and marrow recovery.^(1,6-10) Gabús et al. evaluated this relationship in the Hematology Service of Hospital Maciel in 1999⁽¹¹⁾ and it was re-analyzed in 2004 by Borelli et al. (data not published). It was concluded that the optimal dose for ASCT is 3 to 5 x 10⁶ CD34⁺ cells/Kg. However, ASCT can also be performed with a CD34⁺ cell dose of between 1.5 and 3 x 10⁶ CD34⁺ cells/Kg; a slight delay in platelet engraftment was observed in these cases, which in this study did not show an impact on transplant related morbidity or mortality.

The Hematology Service of the Hospital Maciel has used Filgen JP (Clausen Filgrastim) as the only HPC-mobilizing agent in the ASCT program from January 2002 to the date of this article, uninterruptedly. This same group of authors performed a descriptive and retrospective evaluation of the use of Filgen JP (Clausen Filgrastim) as mobilizing agent during this period.⁽⁵⁾ This work showed:

- Optimal numbers of CD34⁺ cells (between 3 and 5 x 10⁶ CD34⁺ cells/Kg) could be obtained by apheresis after mobilization with Filgen JP (Clausen Filgrastim).

- A median of two apheresis procedures was needed to obtain the desired number of CD34⁺ cells. One or two procedures were sufficient in 61.7% of mobilizations, while three aphereses were needed in 18.5% of cases.

- In 9.8% of mobilizations it was not possible to reach adequate counts of CD34⁺ cells; these patients were rescued with a new mobilization procedure: second mobilization with

growth factors, growth factors plus chemotherapy or bone marrow harvesting.

- Among patients who showed complex mobilization, the following frequent characteristics were identified: age above 50 years, multiple myeloma as underlying malignancy and a disease not in a remission state at the time of ASCT.

Aim

The aim of the current retrospective study was to compare stem cell mobilization using different brands of filgrastim. This Service has only used Filgen JP (Clausen Filgrastim) as the mobilizing cytokine since January 2002. Patients mobilized before that date received different brands of filgrastim.

Methods

A descriptive, longitudinal and retrospective study was performed of data from May 1997 to April 2006 of the ASCT program of the Hematology Service of Hospital Maciel. The data sources were as follows:

- Centralized medical records
- Data registry forms of the ASCT program
- Individual files from the hemobiology laboratory
- ASCT discharge summaries

One hundred and fifty-seven stimulation-apheresis procedures performed on 149 patients were included in this study (eight double mobilizations). Mobilizations of healthy donors for allogeneic SCT were not evaluated in this work.

Inclusion criteria

The inclusion criterion was stem cell mobilization for ASCT in the Hematology Service of Hospital Maciel with filgrastim as the only mobilizing cytokine between May 1997 and April 2006.

Characteristics of the population

One hundred and fifty-seven mobilizations were divided into two groups, according to the period of time in which the mobilization was performed and therefore the origin of the mobilizing agent. Group A corresponds to patients mobilized with different brands of filgrastim between 1997 and 2001 (n = 76) and Group B corresponds to subjects mobilized with Filgen JP (Clausen Filgrastim) between 2002 and 2006 (n = 81).

Population characteristics (age, gender, underlying malignancy, chemotherapy lines prior to mobilization, previous radiotherapy and disease status at mobilization) are detailed in Table 1.

Indications for ASCT were as follows: non-Hodgkin lymphoma 66 (42%); multiple myeloma 29 (18.5%); Hodgkin's lymphoma 28 (17.8%); acute myeloblastic leukemia (AML) 23 (14.6%); acute lymphoblastic leukemia (ALL) seven (4.6%) and solid tumors four (2.5%).

Table 1 - Characteristics of the study population				
	All mobilizations (n=157)	Group A (n=76)	Group B (n=81)	p-value
Gender (n)				
Men	86	43	43	0.78
Women	71	33	38	
Age (years) mean [range]	41.5 [15-66]	38.7 [15-61]	44.1 [15-66]	0.017
Indication of ASCT (n) (%)				
NHL	66 (42)	35 (46.1)	31 (38.3)	0.09
MM	29 (18.5)	9 (11.8)	20 (24.7)	
HL	28 (17.8)	14 (18.4)	14 (17.3)	
AML	23 (14.6)	14 (18.4)	9 (11.1)	
ALL	7 (4.6)	4 (5.3)	3 (3.7)	
ST	4 (2.5)	0	4 (4.9)	
Chemotherapy lines prior to mobilization* (n)				
1 line	81	40	41	0.13
2 lines	32	10	22	
3 or more lines	11	7	4	
No data	3	1	2	
Total	127	58	69	
Previous radiotherapy (n)				
No	133	63	70	
Yes	24	13	11	
Disease status at mobilization (n)				
Complete remission	81	53	28	0.00002
Partial remission	67	19	48	
Progressive disease	9	4	5	
Mobilization strategy (n)				
Filgrastim	134	64	70	0.86
Chemotherapy plus filgrastim	23	12	11	

Group A: patients mobilized with different brands of filgrastim (1997-2001); Group B: subjects mobilized with Filgen JP (Clausen Filgrastim) (2002-2006); NHL: non-Hodgkin lymphoma; HL: Hodgkin's lymphoma; MM: multiple myeloma; AML: acute myeloblastic leukemia; ALL: acute lymphoblastic leukemia; ST: solid tumor

*First, second and third or subsequent lines of treatment were evaluated in patients with NHL, HL, MM and ST. This variable was not evaluated in patients with acute leukemias given the characteristics of chemotherapy protocols usually administered with these disorders

Eighty-one stimulation-apheresis procedures (51.6%) were performed in patients whose underlying disorder was in complete remission. In 67 cases (42.7%), corresponding mostly to lymphoproliferative disorders and multiple myeloma, mobilization was achieved in partial remission. Nine patients (5.7%) had progressive disease at the time of mobilization.

As mobilization results are influenced by previous chemotherapy exposure (one, two or more treatment lines) some considerations must be taken into account. Characteristics and intensity of chemotherapy regimens for acute leukemias and chronic lymphoproliferative disorders are not comparable. When considering previous chemotherapy exposure, only chemotherapy lines received by patients with lymphoma, myeloma and solid tumors (n = 127) are shown in Table 1 with AML and ALL patients (n = 30) being excluded in this analysis. In 81 mobilizations, patients had received

only one treatment line prior to stimulation with filgrastim. In another 32 mobilizations subjects had received two chemotherapy lines and 11 patients had been exposed to three or more treatment lines. Twenty-four patients (15.3%) had also received radiation treatment at some time before mobilization.

When characteristics of Groups A and B were compared, no statistically significant differences were found regarding gender, ASCT indication, previous chemotherapy lines, exposition to radiotherapy or mobilization strategy.

However the following statistically significant differences (p < 0.05) were found:

- Higher age in Group B;
- Higher number of subjects in partial remission in Group B; the number of patients in complete remission was significantly higher in Group A (Table 1).

Mobilization protocol

The mobilization protocol consists on filgrastim (10 mcg/Kg/day subcutaneously) divided in two daily doses during five consecutive days. If the number of CD34⁺ cells in peripheral blood on the fifth day is above 10 cells/mm³, harvesting by apheresis is initiated. If this number is not reached, stimulation is continued but increasing the dose of filgrastim and maintaining it until reaching the desired count for harvesting.

The use of chemotherapy together with the growth factors as mobilization strategy is reserved for the following situations:

1. Patients who are expected to have difficulty in obtaining CD34⁺ cells.

2. Patients in whom an additional therapeutic benefit in respect to their underlying disease is expected when receiving a cycle of high dose chemotherapy as mobilization protocol.

3. Failure of filgrastim-based mobilization.

In these cases, the dose of filgrastim is 5 mcg/Kg/day and administration is started after chemotherapy is finished (day +1 for high dose cyclophosphamide, day +5 in other chemotherapy protocols).

In case of failure in reaching the adequate count of CD34⁺ cells in peripheral blood, the patient is withdrawn from the mobilization program and one of the following options must be chosen: repeat the mobilization, bone marrow harvesting, or suspend inclusion in the ASCT program.

In the analyzed population, 85% of mobilizations (134) were performed after treatment with filgrastim and 15% (23) after chemotherapy plus filgrastim.

Apheresis protocol

The apheresis procedures were carried out with a Cobe Spectra apheresis system, with continuous flow and processing four blood volumes at a high flow (120 mL/minute) requiring variable duration (four to six hours each procedure).

CD34⁺ cell count protocol

CD34⁺ cells (both in peripheral blood and apheresis products) were quantified by flow cytometry following the modified International Society for Hematotherapy and Graft Engineering (ISHAGE) 1996 method (CD34⁺ cell count with a SS/CD34 PE cytogram on a previous selection with CD45 FITC).⁽¹²⁾

Statistical analysis

The non-parametric Mann-Whitney test was used to compare differences, as the clinical parameters had an asymmetric (non-Gaussian) distribution. Four groups were created using a cluster analysis technique (Ward algorithm

ascending hierarchical clustering), which ensures a minimum intra-group variance and a maximum inter-group variance. The variables used were: age, administered dose of filgrastim, number of apheresis and harvested CD34⁺ cells.

Results

Considering all mobilization procedures (157) the mean total dose of filgrastim was 105 mcg/Kg (25-300 mcg/Kg). CD34⁺ cells in peripheral blood on the fifth day of stimulation were quantified only in 54 mobilization procedures (34%). This lack of data was because this parameter was not systematically evaluated in the first stages of the ASCT program. When CD34⁺ cell count in peripheral blood on the fifth day of stimulation was measured, the mean value was 44 CD34⁺ cells/mm³ (1-130).

A median of two apheresis sessions was needed (range: 1-6; standard deviation – SD = 1.2248) to obtain products with the required number of CD34⁺ cells.

An adequate cellularity was harvested in 93% of mobilizations (146/157). In 29.3% of mobilizations (46/157) the goal was achieved with a single apheresis; in 30.6% of mobilizations two aphereses were needed (48/157). This means that in almost 60% of the mobilizations an adequate product was collected with one or two apheresis (94/157). Three to six apheresis were required in 33.1% of the mobilizations.

In another 11 mobilizations (7%) the adequate CD34⁺ cell count was not reached ($0.05 - 1.41 \times 10^6$ CD34⁺ cells/Kg). In other words, these mobilization procedures failed; procedures in which the obtained product did not reach 1.5×10^6 CD34⁺ cells/Kg was considered a failure, according to the aforementioned criteria. The strategy used in these patients was diverse:

- In eight cases the patients were submitted to a second mobilization with filgrastim (in one of them molgramostim was also used in the second mobilization). Considering both first and second mobilizations, a sufficient number of cells was achieved.

- In one case the patient was re-mobilized with filgrastim associated to chemotherapy;

- In one case a bone marrow harvest was performed; So in ten cases an adequate CD34⁺ cellularity was reached, allowing an autologous transplant. In the other case the patient was included in the allogeneic transplant program.

Considering the 157 mobilization procedures, an average of 4.98×10^6 CD34⁺ cells/Kg was harvested [range: $0.05 - 30 \times 10^6$ CD34⁺ cells/Kg]. Figure 1 shows the distribution of number of harvested cells in relation to the filgrastim dose.

When these results are analyzed separately for Groups A and B, no significant differences were seen regarding the number of aphereses and harvested CD34⁺ cells and number of mobilization failures. Total dose of filgrastim was significantly lower in Group B (Table 2).

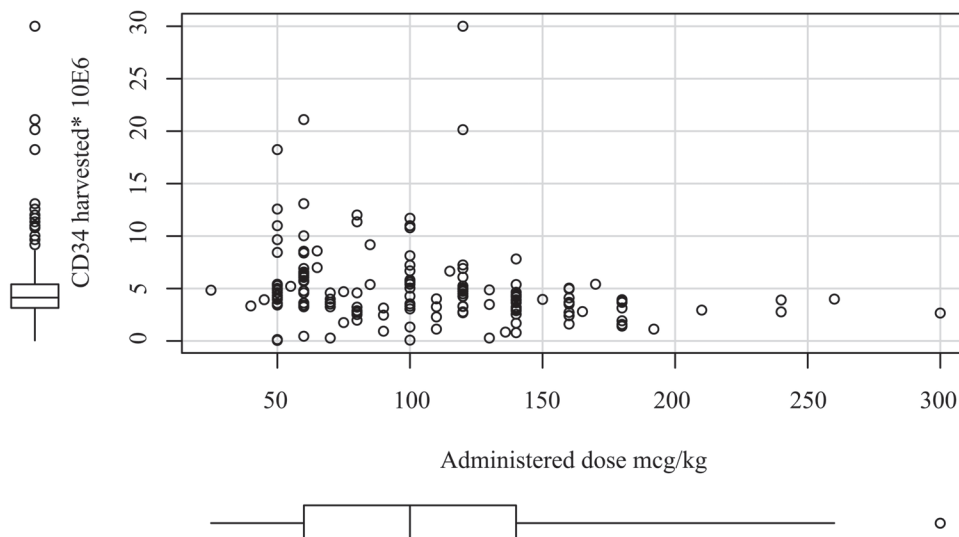


Figure 1 – Harvested CD34⁺ cells and filgrastim dose

Table 2 - Results of progenitor cell mobilization and harvest

	All mobilizations (n=157)	Group A (n=76)	Group B (n=81)	p-value
Filgrastim dose (mcg/Kg)	105 (25-300)	135 (55-300)	78 (25-210)	< 0.001
Apheresis (median)	2 (1-6)	2 (1-6)	2 (1-5)	0.588
Harvested CD34 ⁺ cells (x 10 ⁶ /Kg)	4.98 (0.05-30)	5.25 (0.07-30)	4.73 (0.05-18.2)	0.33
Mobilization failure (n)	11/157	3/76	8/81	0.07

Discussion

The results obtained in this study confirm that stimulation with filgrastim in patients who are candidates to ASCT is a feasible method to obtain sufficient stem cells for an adequate autograft. The results obtained in this analysis confirm those already observed in an earlier study with fewer patients.⁽⁵⁾

As in the analyzed period there were two groups of patients differentiated by the source of stimulating cytokine (different brands of filgrastim versus Filgen JP [Clausen Filgrastim]), a comparison between these two groups was carried out. As described, Groups A and B are comparable in terms of gender, underlying disorder, chemotherapy lines, previous exposure to radiotherapy and mobilization strategies. Regarding these variables, the following must be taken into consideration:

a) It is known that in certain disorders, such as multiple myeloma, mobilization is more complicated. Although there were no significant differences in the distribution of diseases in each group, there were more myeloma patients in Group B.

b) No significant differences were found between Groups A and B in terms of previous treatment lines, which means that in none of the groups the patients received a more intense treatment.

c) Mobilization with chemotherapy plus filgrastim generally means that the total accumulated dose of filgrastim is higher than in cases in which the mobilization was based exclusively on filgrastim. This is because there exists a post-chemotherapy aplasia of variable duration, during which filgrastim is used on a daily basis until marrow recovery.

Given the variables in which significant differences between groups were detected, the following must be noted:

a) There is no particular explanation for the difference found in the mean ages of patients in groups. While these groups are separated in time, the age criteria for selecting patients for ASCT were not modified between the two periods of the study.

b) Regarding the differences found in disease status at the time of mobilization, in Group B there were more patients that reach mobilization in partial remission compared to Group A. During the first years of the ASCT program, indications for autotransplant covered a wider variety of diseases in first complete remission (particularly lymphoproliferative disorders). Thus, Group B patients present a less favorable state at the time of mobilization; it is still debated whether or not being in remission affects the results of the mobilization-harvesting procedure.

When analyzing the results of mobilizations (Table 2) it can be seen that there are no significant differences between groups regarding the number of apheresis needed and the

total harvested CD34⁺ cells. However, there is a clear difference in the total dose of filgrastim required; Group B mobilized and harvested with a significantly lower dose of filgrastim.

The 157 stimulation-apheresis procedures were divided into four groups using a cluster analysis method that took into account similar behavior to stimulation.

– Cluster 1 (n = 19; 12%), average age of 34 years old and an average dose of filgrastim of 77 mcg/Kg. A median of one apheresis was required and 12.7 x 10⁶ CD34⁺ cells/Kg were harvested.

– Cluster 2 (n = 43; 27.4%), average age of 27 years old. Average administered dose of filgrastim in this group was 89 mcg/Kg. A median of two aphereses was required in this group to achieve desired cellularity with an average harvest of 4.5 x 10⁶ CD34⁺ cells/Kg.

– Cluster 3 (n = 53; 33.8%), average age of 52 years old, and an average dose of filgrastim of 90 mcg/Kg and a median of two aphereses to harvest an average of 4.2 x 10⁶ CD34⁺ cells/Kg.

– Cluster 4 (n = 42; 26.8%), average age of 44 years old. These patients received higher doses of filgrastim (average 156 mcg/Kg) and required a median of four aphereses to obtain a cellularity of 3 x 10⁶ CD34⁺ cells/Kg (Figure 2).

Patients in Cluster 1 show an optimal performance at mobilization: a low requirement of filgrastim, a minimum number of apheresis and CD34⁺ harvested cellularity above required range. Patients in Clusters 2 and 3 show an intermediate behavior, while patients in Cluster 4, although harvesting was possible and the patients reached an adequate count of CD34⁺ cells, they do so based on a high requirement of filgrastim and more apheresis procedures.

Table 3 details characteristics of each cluster, as well as their distribution within Groups A and B. Clusters 1, 2 and 3 shows a favorable behavior in terms of filgrastim dose, number of required apheresis and harvested cells. Most of these procedures belong to Group B. Subjects in Cluster 4 exhibit the worst performance in terms of filgrastim dose, apheresis number and cellularity and were mostly in Group A.

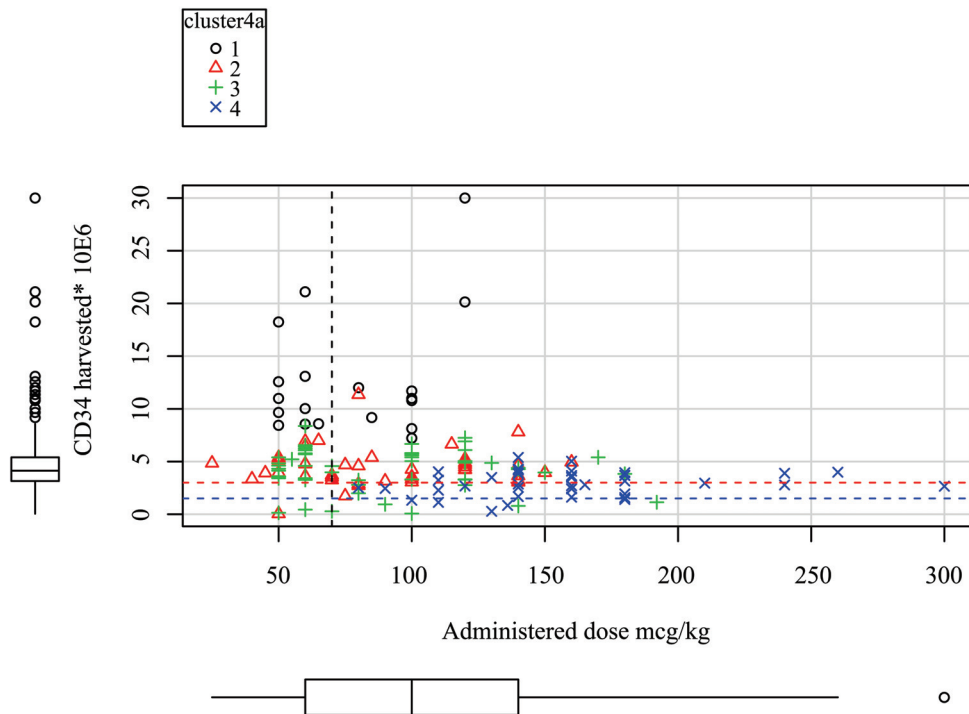


Figure 2 – CD34⁺ cell count in relation to filgrastim dose. Group Analysis (Cluster Analysis)

Table 3 - Distribution of the mobilization-apheresis procedures through cluster analysis							
	n	Age (years)	Filgrastim dose (mcg/Kg)	Number of aphereses (median)	Harvested CD34 ⁺ cells (x 10 ⁶ /Kg)	Group A (n)	Group B (n)
Cluster 1	19	34	77	1	12.7	8	11
Cluster 2	43	27	89	2	4.5	17	26
Cluster 3	53	52	90	2	4.2	24	29
Cluster 4	42	44	156	4	3	27	15
Total	157	41	105	2	5	76	81

Conclusions

Stimulation with filgrastim is an adequate method to obtain stem cells in patients for ASCT.

The retrospective and comparative analysis shows that the origin of the cytokine used as the mobilizing agent is an element to be taken into consideration (among other facts) at the time of evaluating the results of the stem cell mobilization-harvest procedure.

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