BAOJ Paediatrics
An Open Access Journal

BIO ACCENT

BAOJ Paediat
Research Article
Volume 6

Mobilizing stem cells in children with cancer: When G-CSF is not enough. The role of plerixafor

Catalina Montoya Tamayo[1]*; Sofía García Williams, MD[1]; Inés Gómez Seguí, MD[1]; Carolina Fuentes Socorro, MD[2]; Bárbara Torres Guerola, MD[1]; José María Fernández Navarro, MD[2]

[1]Department of Pediatric Hematology and Oncology, Hospital Universitario y Politécnico La Fe, Valencia-Spain. Av. Fernando Abril Martorell s/n, Valencia, Spain.

[2]Department of Pediatric Hematology and Oncology, BMT Unit, Hospital Universitario y Politécnico La Fe, Valencia-Spain. Av. Fernando Abril Martorell s/n, Valencia, Spain.

***Corresponding Author: Catalina Montoya Tamayo**

Department of Pediatric Hematology and Oncology, Hospital Universitario y Politécnico La Fe, Valencia-Spain. Av. Fernando Abril Martorell s/n. Valencia, 46026 Spain.

Tel: +34 680174015; Email: cata_montoyat@hotmail.com; montoya_cat@gva.es

Abstract

The incidence of mobilization failure in children is 10-30%, mainly explained by poor bone marrow function due to treatment toxicity or the underlying disease itself. For tandem-auto stem cell transplant a greater number of hematopoietic stem cells must be collected, sometimes it can be difficult to get. Plerixafor is an antagonist of CXCR4 that facilitates the mobilization of hematopoietic stem cells from bone marrow to peripheral blood. Its use seems safe and effective in children, but evidence is lacking.

We report a retrospective review of 28 children mobilized with G-CSF and plerixafor from 2009 to 2017. Median age was 5.2 years (range 1-15) and median weight 18.25 Kg (range 11-58.6).

All patients except one (96.5%) were adequately mobilized with a pre-apheresis count of CD34+/uL >15 and a collection of CD34+x10^6/kg >2.5. No side effects were reported. Twenty-six children were underwent auto stem cell transplant, achieving a complete graft in all cases, with a median time to engraftment of 12 days for neutrophils and 17 days for platelets.

In our experience, the use of G-CSF + plerixafor is safe and effective in children, and allows to harvest adequate doses of CD34+, even in patients who previously did not respond to mobilization with G-CSF.

Citation: Tamayo CM, Williams SG, Seguí IG, Socorro CF, Guerola BT, et al. Mobilizing stem cells in children with cancer: When G-CSF is not enough. The role of plerixafor. BAOJ Paediat. 2022; 6(1): 1001.

Received: Feb 07, 2022
Accepted: Mar 21, 2022
Published: Mar 29, 2022
Archived: www.bioaccent.org

Keywords: Plerixafor, stem cells mobilization, apheresis, children, autologous stem cell transplantation, mobilization failure.

Introduction

Autologous stem cell transplant (ASCT) in pediatric patients has limited indications. The most frequent are high risk solid tumors after megatherapy such as high-risk central nervous system (CNS) tumors, refractory or relapsing lymphomas, high-risk neuroblastoma (HRNB) and high-risk Ewing's Sarcoma, among others [1-3]. In some cases they require a tandem-ASCT.

The preferred source for the collection of hematopoieticprogenitors (HSC) for ASCT is peripheral blood [2,4]. In children central venous accesses are preferred due to the need of continuous flow during apheresis, not possible with some pediatric peripheral lines especially in children with low weight [6-9].

The mobilization schemes used are based on G-CSF combined or not with chemotherapy [1]. A minimal amount of 2x106 CD34+/kg ensures the engraftment in each ASCT, and a higher dose (≥5x106 CD34+ cells/kg) is related to a faster recovery of neutrophils and platelets [4].

These schemes are usually effective to harvest an optimal dose of CD34+/kg, nevertheless is estimated that the frequency of mobilization failure in children is approximately 10-30% [2-5].

There are several factors that influence the mobilization of HSC, such as: age, weight, type and dose of growth factor4 and above all, poor bone marrow function. The latter due to the disease itself, bone marrow infiltration or cumulative toxicity of previous treatments, mainly the number of cycles of chemotherapy and irradiation on hematopoietically active bone [2,5].

The CD34+ count in peripheral blood pre-apheresis is the best predictor of apheresis success. Counts of >20 CD34+/uL predict adequate collection of HSC in 2-3 apheresis procedures and counts >50 CD34+/uL an adequate collection with only 1 or 2 procedures.4 Mobilization failure is defined as CD34+ <10/uL in peripheral blood during mobilization [2].

Plerixafor is a selective and reversible antagonist of CXCR4, an anchoring protein of the HSC to the stroma of the bone marrow. The inhibition of the union of SDF-1alpha (stromal-derived growth factor) to its CXCR4 receptor facilitates the rapid mobilization of HSC from bone marrow to peripheral blood. In children, a combined mobilization scheme with subcutaneous G-CSF 10-20 ucg/kg every 12-24h for 4 days and subcutaneous plerixafor 240ucg/kg, 10-12h before to apheresis is used.

The available evidence on the use of plerixafor in children is limited. We would like to share our experience with the use of plerixafor for mobilizing HSC in children with cancer.

Patients and methods

We presented a retrospective and descriptive review of the use of plerixafor in children candidates to ASCT treated in the Oncology Unit of our hospital, between December 2009 and December 2017.

The plerixafor was indicated in the following cases:

- Previous failure of mobilization with G-CSF.

- Potential poor mobilizers, defined as patients with advanced disease (>2 complete remission), or submitted to two or more lines of treatment.

- Tandem-ASCT indication: High risk Medulloblastoma or PNET in children under 5 years (3 ASCT in tandem), Germ Cell Tumor of CNS (2 ASCT in tandem) and HRNB that could require 1-2 ASCT (one of them after therapeutic MIBG).

The mobilization scheme consisted in subcutaneous administration of G-CSF 10-15 ucg/kg/day in the morning, for 5 consecutive days and plerixafor 240 ucg/kg on the 4th day at night (10 -12h before the apheresis).

On the 5th day in the morning, the CD34+ count in peripheral blood was measured. If the CD34+ count was ≥10/uL, the apheresis was performed. Patients with CD34+ count <10/uL continued with G-CSF and plerixafor the same as the 4th day of mobilization until obtaining an adequate pre-apheresis count or for maximum 3 days.

The mononuclear cell harvest was performed in Cobe Spectra or Spectra Optia equipment in continuous mode (CMNC) or by cycles (CMN), at least two volemias were processed and citrate was used as anticoagulant (ACD-A). Apheresis was performed with double-lumen central venous catheter (Hickman). In patients <25 kg, the machine was primed with a irradiated red blood cells diluted with physiological solution until the patient's hematocrit was obtained.

The target cellularity was 2x106CD34+/kg for each planned ASCT, considering an ideal count ≥5x106CD34+/kg for each ASCT. In case of insufficient harvest, patients received G-CSF and plerixafor until obtaining an adequate collection of CD34+/kg o for a maximum of 3 procedures.

The following variables were collected: age, sex, weight, diagnosis and stage of the disease, previous treatments, previous mobilizations, mobilization outcome, number of plerixafor doses required, adverse effects related to plerixafor, number of apheresis procedures, apheresis product cell counts, number of ASCT performed and days to engraftment.

Data collected have been summarized by mean (standard deviation) and median (1st and 3rd quartiles) in the case of numerical variables, and by absolute frequency (relative frequency) in the case of qualitative variables.

Due to the limited sample size to evaluate possible variables to predict the response to plerixafor, the Bayesian perspective was used.

Plerixafor was requested as "Compassionate Use". Informed consent by the parents or legal guardians of the patients was obtained.

Results

Twenty-eight children were mobilized with G-CSF and plerixafor. The median age was 5.2 years (3.2 - 8) and median weight 18.3 kg (14 - 28.2). Thirteen (46.4%) patients had CNS tumors, 10 (35.7%) HRNB, 2 (7.1%) Hodgkin`s Lymphoma and 3 (10.7%) other solid tumors.

At the time of apheresis, half of the patients (53.5%) had complete remission of their disease, nine (32.1%) patients had partial response to treatment and four (14.2%) had active or progressive disease.

All patients received treatment with chemotherapy with a median of 4 cycles (2 - 8) and 17.8% (n= 5) also received local radiotherapy (1 CNS and 4 thoraco-abdominal). Patient's characteristics are detailed in Table 1.

Table 1: Demographic characteristics and underlying diseases.

Variable	n = 28
	Mean (SD) /n (%)
	Median (1st - 3rdQ)
Sex	
Male	20 (71.5%)
Female	8 (28.5%)
AGE (years)	6.1 (3.6)
	5.2 (3.2 - 8)
WEIGHT (kg)	22.08 (10.9)
	18.25 (14 - 28)
Diagnostic	
CNS tumors	13 (46,4%)
HRNB	10 (37,7%)
Hodgkin`s Lymphoma	2 (7,1%)
Refractary Burkitt Lymphoma	1 (3,5%)
Metastasic Ewing`s Sarcoma	1 (3,5%)
Metastasic Retinoblastoma	1 (3,5%)
Status Disease	
1º CR	10 (35.7%)
2º CR	4 (14.3%)
≥ 3º CR	1 (3.5%)
Partial response	9 (32.1%)
Active disease / progression	4 (14.3%)
Previous Treatment	
Chemotherapy	23 (82%)
Chemotherapy + radiotherapy	4 (14.3%)
Chemotherapy + radiotherapy+ ASCT	1 (3.5%)

CR: Complete remission

Plerixafor was used as first line strategy in 19/28 patients (67.8%): Nine (32.1%) patients with tandem-ASCT indication (7 CNS tumors and 2 HRNB) and ten (35.7%) patients that were potential poor mobilizers (6 HRNB, 1 Hodgkin lymphoma in 3CR, 1 metastatic retinoblastoma, 1 Ewing's sarcoma in 2RC, 1 refractory Burkitt's lymphoma). Plerixafor was indicated as second line due to previous mobilization failure in 9/28 patients (32.1%), 4 HRNB, 4 CNS tumors and 1 Hodgkin lymphoma in 2CR.

To achieve adequate mobilization, 22 (78.5%) patients received only 1 dose of plerixafor, 3 patients received 2 doses and 2 patients received 3 doses. No adverse events related to plerixafor administration were reported.

There was only one mobilization failure in a patient with HRNB and previous failure of mobilization with G-CSF, who underwent mobilizations with plerixafor in two times with a pre-apheresis CD34+/uL counts in peripheral blood of 0/uL. The remaining patients had a median CD34+/uL in peripheral blood pre-apheresis was 85 cells/uL (43 – 208). In all of them, the overall harvest of apheresis was adequate, with a median collection of CNTx108/kg of 8.43 (5.21 - 11.18) and of CD34+x106/kg of 6.59 (4.25 - 9.48), with a median of 2.03 (0.85 – 3.10) volemias processed. All the data described are summarized in Table 2.

Of the mobilized patients, 70% (19/27) collected >5 CD34+/kg and 30% (9/27) achieved 2-5CD34+/kg. No significant differences were found when comparing both groups.

Table 2: Mobilization and apheresis

Variable	n = 28
	Mean (SD) / n (%) Median (1st - 3rd Q)
Indication of Plerixafor	
Previous mobilization failure	9 (32.14%)
Potentially poor mobilizers	10 (35.71%)
Tandem-ASCT	9 (32.14%)
Plerixafor Number of Doses	
1	22 (78.57%)
2	4 (14.29%)
3	2 (7.14%)
Days of Apheresis	
1	21 (75%)
2	4 (14.29%)
3	3 (10.71%)
PRE-apheresis: CD34+/uL	144.61 (151.3)
	85 (43 - 208)
Total apheresis: CNTx10^8/kg	10.12 (7.18)
	8.43 (5.21 - 11.18)
Total apheresis: CD34x10^6/kg	8.36 (6.61)
	6.59 (4.25 - 9.48)
Processed blood volume	2.01 (0.56)
	2.03 (0.85 – 3.1)

Patients mobilized with plerixafor in the first line collected more CD34+x106/kg. The differences are statistically significant both with the group of poor mobilizers (estimate=6.471, 95% CI [0.879, 12.063], p value 0.025) and in patients with tandem-ASCT indication (estimate=8.622, 95% CI [2.84, 141.404], p value 0.005), with respect to patients with previous mobilization failure, regardless of age and weight. Table 3. There are no significant differences in the collection of CNT/kg collected between the 3 groups.

Were underwent to ASCT 25/28 apheresed patients. One received two ASCT after therapeutic MIBG and one patient with metastatic retinoblastoma did not undergo to ASCT for progression. The median number of infused cells per procedure was 6.59×106CD34+/kg [1,4-10,6]. In all cases, an adequate hematological implant was achieved with a median time of 12 days [11-12] and 17 days [15-21] respectively for neutrophil and platelet engraftment (Table 4).

Table 3: Mobilization and apheresis according to the indication of plerixafor

Variable`	Previous mobilization failure n = 8	Poor mobilizers n = 10	Tandem-ASCT n = 9
	Mean (SD) / n(%)	Mean (SD) / n(%)	Mean (SD) / n(%)
	Median (1st, 3rd Q.)	Median (1st, 3rd Q.)	Median (1st, 3rd Q.)
AGE	6 (4.73)	7.28 (3.69)	5.13 (2.33)
(years)	4 (2.2, 8)	7.5 (4.5, 8)	4 (4, 6.8)
WEIGHT	20.57 (10.99)	25.16 (13.05)	20.18 (8.65)
(kg)	16 (12, 29.5)	22.5 (17.88, 28)	16.8 (14, 24)
CHEMOTHERAPY	5.8 (2.5)	8.9 (3.4)	1.5 (0.68)
(cycle #)	7 (3,8)	8 (6,13)	1 (1,2)
RADIOTHERAPY	2 (25%)	3 (30%)	0 (0%)
NO RT	6 (75%)	7 (70%)	9 (100%)
CD34+/UL	45.9 (21.31)	85.64 (61.91)	297.89 (170.78)
PRE-apheresis	44.3 (37.45, 54)	86.5 (48.1, 93)	317 (177, 374)
CNTx10^8/Kg	10.58 (10.08)	10.91 (6.02)	8.77 (5.33)
	7.4 (3.89, 10.61)	9.61 (6.73, 14.03)	8.12 (4.69, 10.8)
CD34+x10^6/kg	3.68 (1.94)	9.38 (6.19)	11.91 (7.78)
	3.66 (2.7, 4.31)	7.96 (5.33, 9.57)	9.43 (6.6, 15.4)

Table 4: Infused cells and engraftment

Variable	n = 42
	Mean (SD) / n (%)
	Median (1^{st} - 3rd Q)
CNTx10^8/kg infused	5.47 (4.63)
	4.1 (2.69 - 6.54)
CD34+x10^6/kg infused	8.36 (6.61)
	6.59 (4.25 - 9.48)
Viability	89.04 (6.98)
	88 (85 - 94)
Neutrophil graft*	12.35 (3.38)
	12 (11 - 13)
Platelet graft**	19.14 (8.15)
	17 (14 - 21)

*First day of 3 consecutive days with neutrophils >500 / mm^3
**Platelets >20,000/mm^3 after 7 days after the last transfusion

Discusion

In 2009, Fowler et al [10] published the results of a mobilization strategy with G-CSF + plerixafor in patients with previous failure, achieving adequate mobilization in 18/20 patients. Subsequently, different studies in adults confirm the successful mobilization with plerixafor in healthy adults and patients with lymphomas and myelomas [4], and currently international guidelines such as ASBMT [11] and EBMT [12] recommend plerixafor in combination with G-CSF as a standard second-line treatment in adults with mobilization failure with a success rate of 76 - 95% [2,5]. However, to date, few studies have been published in children and there are no specific recommendations for them.

In 2011, Shenoy et al [14] reported 40 cases of children mobilized with plerixafor + G-CSF in 19 centers around the world. Forty-four procedures were performed in 40 patients, of which 33 were in second line due to failure of the HSC harvest after standard mobilization with G-CSF, and in 7 patients, plerixafor was used as rescue in the presence of poor mobilization before the apheresis. The success rate was 70% (31/44 procedures) with only 3 mobilization failures and 10 suboptimal mobilizations with a collection of <2x10e6 CD34 +/kg. There were 16 adverse events probably related to plerixafor, all mild to moderate, mainly gastrointestinal (nausea, vomiting and diarrhea), as well as reaction at the injection site, bone pain, headache and insomnia. Hematological recovery after auto-TPH in these patients was adequate with an average of 9 days for neutrophils.

In addition to these, 126 cases of children mobilized with plerixafor have been published both as first line (rescue in poor mobilizers) [1,4,5,14,15], or as a second line in previous mobilization failures [2,3,13,14] with success rates of 57%-100% and few or no associated adverse events. The largest series are those reported by Teusink et al [3], with 16 children with mobilization failure, who received G-CSF + plerixafor with a mobilization success rate of 87.5%, with no adverse events reported associated to plerixafor treatment; and AA Maschan et al [4], who reported a series of 33 children treated in the same center, who after the failure of mobilization with G-CSF or G-CSF + chemotherapy, received a combined scheme with G-CSF + plerixafor with a failure rate of 6%. The reported toxicity is 26%, mild in all cases. Twenty-four out of 33 patients underwent ASCT with a good hematological recovery with a median engraftment of 12 days for neutrophils and 16 days for platelets [4].

In these series, most patients had a diagnosis of HRNB treated with several cycles of chemotherapy plus/minus radiotherapy or patients with medulloblastoma. That is patients with poor

bone marrow function or with previously failed mobilization with GCSF, who did not collect CD34+ cells enough to undergo ASCT [3-5,13,14].

The most prevalent underlying diseases in our series were high-risk CNS tumors (PNET, medulloblastoma, germ cell tumor), with tandem-ASCT, in whom the plerixafor was used as first line regimen. In second place, patients with HRNB were considered poor mobilizers because they had received several lines of treatment prior to the aferesis. The remaining patients had poor prognosis solid tumors with metastatic, refractory or relapsing diseases that had received different lines of treatment.

Despite of different indications in the use of plerixafor in our series, success rate of mobilization with plerixafor was 96.5%, similar to previously reported in the literature (success rates between 57-100%) [2-4]. There was only a mobilization failure in a patient with HRNB with previous failure of mobilization with G-CSF, who received mobilization with G-CSF + plerixafor in two times, both unsuccessful. Eventually she underwent bone marrow collection of $2.8x10^6$ CD34+/kg and ASCT was performed.

The median cell collection was 6.59x106 CD34+/kg. The majority of patients (78.5%) achieved the target CD34+>$2x10^6$/kg with only one dose of plerixafor and processing 2 volemias. The use of more than one dose of plerixafor did not correlate with indication neither with underlying disease status.

Our cohort included patients requiring tandem transplant for the initial diagnosis that likely would mobilize well without plerixafor. Although this is the group that requires higher cell number to be collected, they are not in the same category as patients with mobilization failures or multiple relapses. Which are associated to poorer bone marrow due to the number of treatments received previous to the apheresis.

The incidence of adverse effects associated with the use of plerixafor in children is low, with mild symptoms such as local reactions at the site of injection, gastrointestinal (nausea, vomiting and diarrhea) or neurological (dizziness, headache or nightmares) [4,13]. In our patients plerixafor was well tolerated in all cases, with no reported serious adverse events associated to its use.

After ASCT, patients presented a fast and stable hematopoietic engraftment. Leukocyte engraftment and transfusion needs did not differ from those reported for patients mobilized with G-CSF only. No transplant related mortality <100 days was reported in this series.

Despite the limitations of this retrospective study and the small sample size, we can conclude that plerixafor is a safe and useful alternative in children, which allows adequate mobilization and collection of HSC in patients with previous mobilization failure or potential poor mobilizing.

The use of plerixafor as first line in selected cases, for example patients with tandem-ASCT indication with a high probability of mobilization failure could avoid procedures with failures in the collection of HSC and delays in treatment. Moreover, the improvement in patient's mobilization rate facilitates the possibility of obtaining the target amount of cells with less volume processed in the apheresis equipment, which is an important advantage in low-weight patients.

Declarations

Funding: This study was not funded.

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Chambon F, Merlin E, Rochette Eet al. Mobilization of hematopoietic stem cells by plerixafor alone in children: A sequential Bayesian trial. Tranf Apheres SCI. 2013; 49: 453–58.

2. Emir S, Demir HA, Aksun T, Kara A, Özgüner M, Tunç B. Use of plerixafor for peripheral blood stem cell mobilization failure in children. Tranf Apheres SCI. 2014; 50: 214-18.

3. Teusink A, Pinkard S, Davies S, Mueller M, Jodele S. Plerixafor is safe and efficacious for mobilization of peripheral blood stem cells in pediatric patients. Transfusion 2016: 56; 1402-05

4. Maschan AA, Balashov DN, Kurnikova EEet al. Efficacy of plerixafor in children with malignant tumors failing to mobilize a sufficient number of hematopoietic progenitors with G-CSF. Bone Marrow Transplant. 2015; 50: 1089-91.

5. Patel, Pearson H, Zacharoulis S. Mobilisation of haematopoietic stem cells in pediatric patients prior to autologous trasplantation following administration of plerixafor and G-CSF. Pediatr Blood Cancer. 2015; 62: 1477-80.

6. Hequet O. Hematopoietic stem and progenitor cell harvesting: technical advances and clinical utility. J Blood Med. 2015; 6: 55-67.

7. Sörensen J, Jarisch A, Smorta Cet al. Pediatric apheresis with a novel apheresis device with electronic interface control. Transfusion. 2013; 53: 761–65.

8. Sauer H, Roland H, Ulla L, Ortrud D, Jürgen F. Leukapheresis in children weighing less than 20 kg. Pediatr. Blood Cancer. 2012: 58: 627–29.

9. Pulsipher MA, Levine JE, Hayashi RJ et al.Safety and efficacy of allogeneic PBPC collection in normal pediatric donors: The pediatric blood and marrow transplant consortium experience (PBMTC 1996–2003). BoneMarrowTransplant. 2005; 35: 361-7.

10. Fowler CJ, Dunn A, Hayes-Lattin B et al. Rescue from failed growth factor and/or chemotherapy Hcc mobilization with G-CSF and plerixafor (AMD3100): an institutional esperience. Bone Marrow Transplant 2009; 43: 909-17.

11. Duong HK, Savani BN, Copelan E et al.Peripheral blood progenitor cell mobilization for autologous and allogeneic hematopoietic cell transplantation: Guidelines of the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2014; 20: 1262-73.

12. Mohty M, Hübel K, Kröger N et al. Autologous haematopoietic stem cell mobilisation in multiple myeloma and lymphoma patients: a position statement from the European Group for Blood and Marrow Transplantation. Bone Marrow Transplantation. 2014;49:865–72.

13. Bitan M, Eshel R, Sadot E et al. Combined plerixafor and granulocyte colony-stimulating factor for harvesting high-dose hematopoietic stem cells: Possible niche for plerixafor use in pediatric patients. Pediatr transplantation. 2016; 20: 565-71.

14. Shenoy S, Douglas KW, Korstek Z et al. Plerixafor Is Highly Effective for the Mobilization of Autologous PBSC for Transplant in Children Failing to Mobilize by Conventional Means: International Experience with 40 Children From 19 Centers. Blood. 2011; 118: 1931.

15. Naithani R, Sachdeva M, Rai R, Dayal N. Plerixafor for hematopoietic stem cell mobilization in children with neuroblastoma. Experimental and Clinical transplantation.2016; 3: 358-359.