Received: 1 September 2021 | Revised: 18 October 2021 | Accepted: 11 November 2021

DOI: 10.1002/jca.21952

RESEARCH ARTICLE

Journal of Clinical Apheresis ASFA WILEY

Successful "on-demand" plerixafor for autologous peripheral blood stem-cells transplantation for relapsed/refractory germ cell tumors

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Abstract

Background: Germ cell tumors represent, among solid cancers, a potentially curable disease even if up to 20% to 30% of patients (pts) relapse after first-line treatment especially considering intermediate and poor prognosis groups. In this scenario, patients are candidates for high-dose chemotherapy and autologous stem-cells transplantation as second-line treatment even though stem-cells mobilization potential can be affected by several cycles and regimens of chemotherapy. To date, plerixafor is authorized in poor mobilizer adult pts diagnosed with lymphoma or multiple myeloma and in pediatric solid tumors or lymphoma. Therefore, the use of plerixafor in adult pts with relapsing/refractory GCT is still off label.

Materials and methods: In our study, we describe mobilization and collection of peripheral blood stem cells for 10 pts with germ cell tumors. Six patients underwent plerixafor administration since classified as poor mobilizers based on WBC count (>5.000/μL) and CD34+ cell count (<15/μL) the day before apheresis procedure.

Results: On the first day of apheresis, plerixafor administration in poor mobilizers made possible a remarkable boost of CD34+ cells in such a way to overlap that of good mobilizers' (32/μL vs 35/μL, respectively, $P > .05$).

Conclusion: Therefore, in our experience, plerixafor made a good fraction of poor mobilizer patients eligible for mobilization and collection and able to undergo the predicted autologous stem-cells transplantation; thus, the lack of access to the use of plerixafor in this setting of patients risks jeopardizing an effective treatment, especially in case of poor prognosis.

KEYWORDS
germ cell tumors, plerixafor, stem-cell transplantation

1 | INTRODUCTION

Germ cell tumors (GCT) represent, among solid cancers, potentially curable diseases with a 5-year overall survival (OS) up to 90% based on class risk assessment.[1] However, up to 20% to 30% of patients (pts) relapse after first-line treatment especially considering intermediate and poor prognosis groups.[2]

In this setting, high-dose chemotherapy (HDC) followed by peripheral blood stem-cells (PBSC) collection and autologous stem-cells transplantation (ASCT) resulted in 5-year OS of 65%.[3,4]

Unfortunately, considering that most of these pts are heavily pretreated, undergoing several cycles and regimens of chemotherapy, their capacity to mobilize and collect an adequate amount of PBSC for ASCT, can be compromised.[5]

In this adverse scenario, plerixafor emerged as a molecule capable of increasing PBSC mobilization, in combination with granulocyte-stimulating factor (G-CSF), acting as an antagonist of CXCR4.[6]

Nevertheless, since its approval this drug is authorized by European Medicines Agency (EMA) in poor mobilizing adult pts diagnosed with lymphoma or multiple myeloma and later in pediatric solid tumors or lymphoma. Therefore, adult pts with relapsing/refractory GCT, according to recognized approved use, are still excluded from the chance to gain an advantage from plerixafor, and its use is to be considered an unapproved off-label use.

The optimal time frame to use plerixafor has been evolving gradually since its approval. So far, it has been an essential tool, which made possible the mobilization and collection of PBSC in pts with lymphoma or multiple myeloma who previously failed and thus, allowing them to undergo HDC and ASCT. In the wake of an increasing approval in the use of plerixafor, it has been used an "on-demand" strategy in poor mobilizer pts with lymphoma or multiple myeloma who would otherwise fail PBSC collection because of low CD34+ cells count.[7] In this way, the opportunity to reach the predicted amount of CD34+ cells/kg raised, avoided further mobilization attempts and bone marrow toxicity as well as related costs. In the meantime, it was not a long time before plerixafor raised attention from physicians with off-label use in solid tumors. Results proved plerixafor to be effective in GCT and other solid tumors like Ewing sarcoma and neuroblastoma who failed prior mobilizations with G-CSF alone or in combination with chemotherapy.

Nonetheless, as an off-label drug, "on-demand" plerixafor, in other words the possibility to use it in order to save a mobilization process which otherwise would be declared as failed, did not move in the same direction for solid tumors whose data in literature appear to be lacking and with a consensus recognized only in case of previously failures.[8-13]

In our study, we describe mobilization and collection of PBSC for 10 pts with GCT in the "era" in which plerixafor was available. Among these, 6 pts were considered poor mobilizer according to Gruppo Italiano per Trapianto di Midollo Osseo criteria[14] and underwent plerixafor administration: two of these underwent a previous failed mobilization attempt while the other four pts were at high risk of mobilization failure and collection processes were saved thanks to "on-demand" plerixafor administration.

2 | MATERIALS AND METHODS

We retrospectively analyzed data from 10 consecutive pts affected by relapsed/refractory GCT undergoing mobilization and collection of PBSC from July 2015 to September 2020 in our center. Pts showing no organ impairment or major comorbidities and an ECOG 0-1, were divided into two groups based on plerixafor administration.

Eight pts (80%) underwent mobilization for the first time, while two pts had a previous mobilization failure: one patient only in the latter group was remobilized with a "chemo-free" regimen using G-CSF and plerixafor.

All pts were treated with cisplatin, etoposide, bleomycin (each cycle every 21 days: cisplatin 20 mg/m^2 /die on days 1-5; etoposide 100 mg/m^2/die on days 1-5; and bleomycin 15 mg/m^2/die on days 1, 8, and 15) as first-line treatment while cisplatin, ifosfamide, paclitaxel (TIP) regimen was preferred in relapsed/refractory pts. Moreover, TIP regimen (each cycle every 21 days: cisplatin 25 mg/m^2/die on days 2-5; ifosfamide 1500 mg/m^2/die associated with Mesna on days 2-5; and paclitaxel 250 mg/m^2 on day 1) was also used as mobilization treatment in all pts but one undergone a "chemo-free" regimen. The latter underwent remobilization with G-CSF at a dose of 10 μg/kg on days 1 through 4 administering plerixafor at standard dose of 0.24 mg/kg the evening of day 4 and initiating apheresis on day 5.

Apart from the above patient, G-CSF was added at 5 μg/kg from day 7 until conclusion of stem cells collection.

Starting from the 10th day after the end of mobilization treatment, white blood cell count (WBC) and CD34+ cells count were monitored daily by Siemens ADVIA 2120i hematology analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany) and flow cytometry

with a median time of 13 days to begin apheresis procedure. Poor mobilization was defined as:

1. Peripheral blood CD34+ stem-cells less than 20/μL after adequate mobilization.[14]
2. Total CD34+ cells collected less than 2.0×10^6/kg in ⩽3 apheresis.[14]

After signing an informed consent as off-label use, plerixafor was administered in 6 pts based on WBC count (>5.000/μL) and CD34+ cell count (<15/μL) the day before apheresis procedure.

The dose was 0.24 mg/kg, 8 to 10 hours before apheresis carrying on G-CSF administration. Apheresis was performed according to local guidelines using a double-needle continuous flow cell separator (COBE Spectra until 2017 then replaced by Optia system).

The crucial point is the importance of collecting and infusing an adequate amount of CD34+ cells for each transplant, set in our institution at $>2.5 \times 10^6$/kg, in order to ensure a rapid hematological recovery.

Conditioning regimen included etoposide 750 mg/m^2 and carboplatin 700 mg/m^2 on days −5, −4, and −3 and PBSC infusion on day 0. Support with platelets and red blood cells transfusions was initiated for a platelet count <10.000/μL and for Hb <8 g/dL, respectively. G-CSF was carried out from day 1 until engraftment, defined as neutrophils ≥ 1.000/μL and platelets ≥ 25.000/μL.

Acyclovir and TMP/SMZ were administered as antimicrobial prophylaxis while in case of neutropenic fever, empirical broad spectrum antibiotics were added and modified based on microbiology cultural exams.

2.1 | Statistical Analysis

Statistical analysis was performed using "Graphpad PRISM" Graphpad Software Inc. (San Diego, CA, USA). Standard descriptive statistics were used to describe the characteristics of patients, procedures, and products. The Mann-Whitney test was used to analyze continuous variables. The Chi-square test was selected for the analysis of categorical variables.

Statistical significance was defined by a double-sided *P*-value of $P < .05$.

3 | RESULTS

Results are summarized in Table 1. Plerixafor was administered in 6 pts:2 pts, with a previous failed mobilization attempt, as predicted poor mobilizers[13] while four pts gained an advantage of "on-demand" plerixafor administration in consideration of high risk of failure and thus qualifying them as proven poor mobilizers.[14]

Overall, median age was 29 years old (range 17-46) with a male preponderance (70%).

On the day before apheresis, median CD34+ cells count was 5/μL (range 3-12) in plerixafor group and 30/μL (range 18-75) among all other pts ($P = .010$). On the first day of apheresis, the boost of CD34+ cells to 32/μL (range 13-55) was more remarkable in plerixafor group rather than the mild increase of median CD34+ cells to 35/μL (range 28-126) in pts in which plerixafor was not administered ($P > .05$).

Median total number of CD34+ cells collected was 6.3×10^6/kg (range 3.27-8.09) in plerixafor group while 5.55×10^6/kg (range 4.64-11.7) among all the others ($P > .05$).

The median total blood volume processed was 3.1 (range 2.3-4.4) and the median number of aphereses necessary to collect the CD34+ cell doses for 1 or 2 ASCT predicted was 2 (range 1-3) independently from plerixafor administration: only two of the six pts in plerixafor group needed one and three procedures while one of the four pts needed one procedure only in the other group. A higher total blood volume was processed in case of a higher chance to achieve the cell goal predicted.

These data were further validated comparing pts who gained an advantage of plerixafor administration with all of our GCT cases mobilized even previous plerixafor approval itself (17 pts). In this scenario, median total number of CD34+ cells collected still did not prove any statistical significance if compared to plerixafor group ($P > .05$).

All pts succeeded in yielding a sufficient amount of CD34+ cells to undergo at least one ASCT while five of the six pts and two of the four pts in plerixafor group and nonplerixafor group, respectively, reached an amount of CD34+ cells sufficient for two ASCT.

No adverse effects were reported in any patients.

ASCT was performed in six pts, one of which undergoing tandem ASCT while remaining pts did not proceed to ASCT because of myelodysplastic syndrome (10%), progressive disease (20%), change of therapeutic approach (10%).

Median time required for neutrophils and platelets recovery (PMN $> 0.5 \times 10^9$/L; platelets $> 20 \times 10^9$/L) was 10 days (range 9-10) and 13 days (range 12-17), respectively, in the plerixafor group, while two pts underwent ASCT without the aid of plerixafor with time of neutrophils and platelet engraftment of 9.5 days (range 9-10) and 15.5 days (range 14-17),

TABLE 1 Characteristics of patients and cell collections

	No Plerixafor	Yes Plerixafor	*P*
No. of patients	4	6	n.a
Gender (M/F)	3/1	4/2	ns
Median age (range) (years old)	28 (28-29)	28.5 (17-46)	ns
Median n. of previous chemotherapy lines (range)	1 (1)	1 (1-2)	ns
Median n. of previous chemotherapy cycles (range)	5.5 (5–6)	6 (5-10)	ns
Median CD34+ cells the day before apheresis (range) (n/μL)	30 (18-75)	5 (3-12)	.010
Median CD34+ cells the day of first apheresis (range) (n/μL)	35 (28-126)	32 (13-55)	.610
Median CD34+ cells collected (range) ($\times 10^6$/kg)	5.55 (4.64-11.7)	6.3 (3.27-8.09)	ns
Transplant cell dose collected	1.5 (1–2)	2 (1-2)	ns

Abbreviations: n.a., not applicable; ns, not significant.

respectively. Median time to reach was 18.7 days and 27.2 days, respectively.

4 | DISCUSSION

Plerixafor approval and its wide use in pts with multiple myeloma and lymphoma[15] aroused attention even in extra-hematological field until recent approval among pediatrics pts with solid tumors.

Early plerixafor adoption aims to make effective a mobilization that is going to fail. Indeed, the deferral of the use of plerixafor to a subsequent cycle of mobilization would be burdened by a decrease rate of success causing further toxicity and actually with a minimal impact on the underlying disease.

In our experience, the use of plerixafor made eligible for collection procedures even pts considered poor mobilizers because of an adequate amount of WBC but insufficient CD34+ cells count. In this setting of pts, the use of plerixafor boosted CD34+ cells count so that, on the day of collection, the statistical difference with all the other pts was nullified.

It is now widely established the role of ASCT as a salvage regimen in relapsed/refractory GCT.[16]

In this setting, pts are heavily pretreated and undergone different cycles and lines of chemotherapy with a stem-cells mobilizing potential inevitably inferior. Especially in the light of a greater amount of CD34+ cells needed for double ASCT, a prompt action may be due to improve the whole process: the chance to increase the blood volume processed may be a first step to make but with a limited potential due to low CD34+ cells count for which plerixafor only may overcome the situation.

Indeed, the use of plerixafor allowed successful mobilizations in 86% of cases with GCT increasing the number of pts who proceeded to ASCT and thus with an increased OS.[17]

Nonetheless, as matter-of-fact, GCT are still excluded from the chance to take an advantage of plerixafor administration for which is still lacking an official indication.

In our clinical records, 6 pts with GCT out of 10 were considered poor mobilizers.

In this setting, "on-demand" off-label use of plerixafor proved to be a safe and effective mobilization approach which made possible to collect an adequate amount of CD34+ cells in a situation in which mobilization would have been declared as failed and, as a consequence, pts were excluded from the chance to take an advantage of ASCT.

5 | CONCLUSION

Undoubtedly, a crucial aspect on plerixafor use is surely its high cost; however, costs must be evaluated overall, directly and indirectly. Indeed, an expensive spending during mobilization is adequately balanced out avoiding further mobilization processes and, with rich in CD34+ cells products, reducing hospitalization and toxicity when ASCT was underway.[18]

In terms of benefit-cost ratio, the use of plerixafor has been associated with a reduction in the number of apheresis procedures and the number of additional mobilization attempts, as well as in the average length of hospital stay in favors of a more abundant collection of stem-cells sufficient for 1 or even 2 ASCT, if necessary.[19]

Clearly our data should be considered in view of the retrospective nature of the study and the small sample size. In fact, we are dealing with a small subset of patients who are unlikely to become numerous in a

single center.[8] On the other hand, precisely because of the small number of patients, further evaluation and data are needed to enhance our understanding in this setting of patients in order to provide a rationale for plerixafor approval in poor mobilizing pts with GCT. The lack of access to the use of plerixafor in this category of patients risks being an obstacle to modern and proven effective treatment especially in case of poor prognosis.

ACKNOWLEDGMENTS

This study was supported by Centro di Ricerca sulle Cellule Staminali Emopoietiche e le Terapie Cellulari, Università Cattolica del Sacro Cuore in Rome. Open Access Funding provided by Universita Cattolica del Sacro Cuore within the CRUI-CARE Agreement.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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How to cite this article: Corbingi A, Metafuni E, Di Salvatore M, et al. Successful "on-demand" plerixafor for autologous peripheral blood stem-cells transplantation for relapsed/refractory germ cell tumors. *J Clin Apher*. 2022;37(1):65-69. doi:10.1002/jca.21952