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Plerixafor for patients who fail cytokine- or chemotherapy-based stem cell mobilization: Results of a prospective study by the Polish Lymphoma Research Group (PLRG)

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Abstract

Autologous hematopoietic stem cell transplantation (autoHSCT) requires collection of sufficient number of hematopoietic stem cells. The goal of this study was to evaluate efficacy of plerixafor used in patients with lymphoid malignancies failing conventional stem cell mobilization.

This was a prospective, non-interventional study. All consecutive patients (n = 109) treated with plerixafor in 11 centers were reported. The drug was used either in case of previous mobilization failure (n = 67) or interventionally, in case of insufficient $CD34^+$ cell output during current mobilization (n = 42). Successful mobilization was defined as resulting in collection of $\geq 2 \times 10^6$ $CD34^+$ cells/kg for single autoHSCT or $\geq 4 \times 10^6$ $CD34^+$ cells/kg for double procedure.

The overall rate of successful mobilization was 55% (55% for single and 56% for double autoHSCT). The median total number of collected $CD34^+$ cells/kg was 2.4 (range, 0-11.5) for patients intended for a single transplantation while 4.0 (0.6-16.9) for double procedure. The number of circulating $CD34^+$ cells increased after the use of plerixafor regardless of baseline values. The median fold increase was 3.3 (0.3-155).

Data from this observational study confirm high efficacy of plerixafor used in routine clinical practice as salvage for patients with lymphoid malignancies failing conventional stem cell mobilization.

Keywords:
plerixafor, stem cell mobilization, multiple myeloma, Hodgkin lymphoma, non-Hodgkin lymphoma.

Background

Autologous hematopoietic stem cell transplantation (autoHSCT) is widely applied for the treatment of patients with lymphoid malignancies [1, 2]. Standard indications include multiple myeloma (MM), Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). While in MM autoHSCT is used as consolidation of first line treatment, for most of lymphoma subtypes it is considered after failure of initial chemotherapy. Currently, autoHSCT procedures are almost exclusively performed using peripheral blood as a source of stem cells, which requires successful mobilization of hematopoietic stem cells [3]. The generally accepted minimal level of $CD34^+$ cells required for rapid neutrophil and platelet recovery after autoHSCT is 2×10^6 cells/kg. However, some data indicate that higher numbers are associated with less need for blood product transfusions and administration of antibiotics [4-10]. In the case of tandem autoHSCT the minimal level of number of collected $CD34^+$ cells is 4.0×10^6 $CD34^+$ cells/kg body weight [4-10].

Several study groups attempted to identify factors associated with the risk of mobilization failure. The first prognostic system was elaborated by Gruppo Italiano Trapianto di Midollo Osseo in 2012 [11]. More recently, Olivieri et al [12] built on real large representative data a score to "rule in" patients at very high risk for poor mobilizers before starting mobilization, allowing changes in clinical management, to avoid highly likely mobilization failure. Predicted poor mobilizer score included as risk factors: increasing age, diagnosis of NHL, positive bone marrow biopsy or cytopenias before mobilization, previous mobilization failure, priming strategy with G-CSF alone, or without upfront plerixafor. Mobilization regimens may either be "steady state" i.e. using granulocyte-colony stimulating factor (G-CSF) alone or may be based on G-CSF in combination with chemotherapy, most frequently cyclophosphamide at the dose of 1.5-7 g/m^2 or lymphoma-specific salvage regimens [9, 10]. Unfortunately, 5-30% of patients fail to mobilize sufficient numbers of $CD34^+$ cells, thus requiring additional attempts [11-13]. New mobilization strategies are being explored including the use of plerixafor, a CXCR4 inhibitor, in combination with G-CSF, with or without chemotherapy. According to initial studies this agent enabled a sufficient $CD34^+$ cell harvest in 64.8-81.6% of proven or predicted poor mobilizers [13-17]. Unfortunately, such treatment is expensive, and therefore should be utilized in patients who are most likely to benefit [18]. Furthermore, attempts to optimize the timing and dosage of plerixafor are still needed [19-24].

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The goal of this study was to evaluate efficacy of plerixafor used in a "real life" setting, i.e. in centers belonging to the Polish Lymphoma Research Group (PLRG). Our intention was also to identify potential prognostic factors in order to optimize the use of plerixafor in future protocols.

Materials and methods

Study design

This was a prospective, non-interventional, observational study, conducted in 11 PLRG centers, which routinely use G-CSF and plerixafor for stem cell mobilization. Data on all consecutive adult patients treated with plerixafor were reported to a central database and included in the analysis. The enrollment period for this study was 15 months or up to a minimum 100 patients enrolled. The required set of data included: demographics, details on diagnosis and preceding chemo- and radiotherapy, details on previous mobilization attempts patients as well as details on current mobilization using plerixafor. The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by the Institutional Ethics Committee. All participating patients provided written informed consent.

Plerixafor use and leukaphereses

In line with the Polish regulations regarding reimbursement of plerixafor by public sources the drug could be used in the following cases:

- unsuccessful previous mobilization defined as collection of < 2.0 × 10^6 $CD34^+$ cells/kg body weight when a single autoHSCT was planned or < 4.0 × 10^6 $CD34^+$ cells/kg body weight when a double autoHSCT was intended,
- despite the use of an adequate mobilization regimen (G-CSF 10 μg/ kg, when given as monotherapy or at least 5 μg/kg, when given after chemotherapy), maximum stem cell count in the peripheral blood was < 10/μL 4-6 days after the onset of G-CSF administration as monotherapy or within 20 days after the onset of administration of chemotherapy in combination with G-CSF.

For the decision to start leukaphereses the number of circulating $CD34^+$ cells was first evaluated on the second day of neutrophil recovery > 1 × 10^9/L in patients who experienced grade 3 or 4 neutropenia or, in the remaining patients, on the first day with increase of neutrophil count. The analysis was done using flow cytometry, according to local protocols. Leukaphereses were started when the $CD34^+$ blood level was at least 10 cells/μl. If the level was not achieved, G-CSF administration was continued or/and plerixafor was added, and $CD34^+$ cell counted until $CD34^+$ level decreased compared to the preceding day.

Exact duration of G-CSF and/or plerixafor administration could vary according to local policies and plerixafor reimbursement schedule. Leukaphereses were performed using Spectra-Optia Apheresis System (Caridia nBCT, Inc., Lakewood, CO, USA) in three centers and using Cobe Spectra (Cobe BCT, Lakewood, CO, USA) in eight centers, according to the manufacturer's protocols for mononuclear cell harvesting, processing 2 blood volumes. The target $CD34^+$ cell yield was > 2 × 10^6/kg before single or 4.0 × 10^6 $CD34^+$ cells/kg body weight before the tandem transplantation.

Study endpoints

The percentage of patients with successful mobilization i.e. who collected ≥ 2 × 10^6 $CD34^+$ cells/kg for single autoHSCT or ≥ 4 × 10^6 $CD34^+$ cells/kg for double procedure, accordingly, was the primary study end-point. The total $CD34^+$ cell yield and the number of leukaphereses needed to obtain the transplant material, as well as fold increase of $CD34^+$ count in peripheral blood before and after 1st plerixafor administration were secondary end-points.

Statistical methods

The statistical analysis included data from all enrolled patients. Chi^2 test analysis was used to evaluate impact of potential prognostic factors with the rates of succesful mobilization. Differences with p values < 0.05 were considered statistically significant. Statistical analysis was performed using Statistica software version 13 (StatSoft Inc., Tulsa, OK, USA).

Results

Patient characteristics

Between October 2015 and February 2017, 109 patients were enrolled in the study, including 64 (59%) men and 45 (41%) women, with median age 55 years (range, 20-71 years). Forty-three patients (39%) had MM while remaining individuals were diagnosed with either NHL or HL. Most patients had been pre-treated with at least 2 lines of systemic therapy, including autoHSCT in 25% of cases. In 67 (61%) patients, plerixafor was used after preceding mobilization failure while in remainig ones, because of insufficient $CD4^+$ cell output, during current mobilization approach. All 109 patients were classified as 'predicted poor mobilizers', according to Gruppo Italiano Trapianto di Midollo Osseo [11, 12]. Detailed patients characteristics are listed in table I. In 91 (83%) cases a single autoHSCT was planned while 18 (17%) patients were intended for a double procedure.

Mobilization with plerixafor

There were 69/109 (63%) participants who received plerixafor in the context of mobilizing or disease-oriented chemotherapy combined with G-CSF. The remaining 40 (37%) patients received G-CSF alone and plerixafor (Tab. II). Among chemotherapy-based regimens intermediate-dose cytarabine with G-CSF was most frequently used, following previous PLRG experience [19, 23, 26]. The median number of plerixafor doses was 2 (range, 1-4). The median single dose was 0.25/kg (range, 0.1-0.48).

Efficacy of mobilization using plerixafor

In 38 (35%) patients the required number of $CD34^+$ cells/kg were collected with a maximum of two plerixafor administrations while the additional 22 patients (20%) requried the subsequent doses. The total sucess rate was 55% (55% for patients intended for single

Table I. Patient characteristics, previous therapy

N	109
Gender	
Male	64 (59%)
Female	45 (41%)
Age, years (median, range)	55 (20-71)
ECOG score	
0	3 (3%)
1	42 (39%)
2	47 (43%)
3	16 (15%)
4	1 (1%)
Diagnosis	
HL	24 (22%)
NHL	42 (39%)
MM	43 (39%)
Bone marrow involvement	81 (74%)
Previous radiotherapy	27 (25%)
Previous bone marrow irradiation	23 (21%)
Previous autoHSCT	19 (17%)
Previous treatment with melphalan	15 (14%)
Previous treatment with lenalidomide	13 (12%)
≥ 2 lines of preceding chemotharapy	80 (73%)
Previous failed stem cell mobilization	67 (61%)
G-CSF alone	18 (17%)
G-CSF + mobilizing CHT	30 (28%)
G-CSF + disease-oriented CHT	17 (16%)
G-CSF + plerixafor	2 (2%)

ECOG – Eastern Cooperative Oncology Group, MM – multiple myeloma; NHL – non-Hodgkin lymphoma, HL – Hodgkin lymphoma, autoHSCT – autologous hematopoietic stem cell transplantation, G-CSF – granulocyte-colony growth factor, CHT – chemotherapy

Table II. Current stem cell mobilization with plerixafor (N = 109)

G-CSF alone	40 (37%)
G-CSF + CHT*	69 (63%)
G-CSF + cytarabine	22 (20%)
G-CSF + cyclophosphamide	14 (13%)
G-CSF + other mobilizing CHT	15 (14%)
G-CSF + disease-oriented CHT	18 (16%)

* CHT: chemotherapy

Table III. Rates of successful CD34+ cell collection according to the number of leukaphereses

No of leukaphereses	Patients with successful mobilization with respect to the total number of 109 cases
1	14 (13%)
2	29 (27%)
3	11 (10%)
4	4 (4%)
6	1 (1%)
7	1 (1%)
Total	60 (55%)

and 56% for those planned for tandem autoHSCT). The number of leukaphereses and respective rates of patients achieving the required $CD34^+$ cell yield is presented in table III. The total number of collected cells was 2.4 (0-11.5) $CD34^+$ cells/kg for patients intended for a single transplantation while 4 (0.6-16.9) $CD34^+$ cells/kg when double procedure was planned.

The number of circulating $CD34^+$ cells increased after the use of plerixafor regardless of baseline values (Tab. IV). The median fold increase was 3.3 (range, 0.3-155). For patients with baseline number of circulationg $CD34^+$ cells < 5/μL, between 5 and < 10/, and ≥ 10/μL, the rates of successful mobilization were 43%, 80% and 55% respectively.

Factors affecting efficacy of mobilization with the use of plerixafor

A univariate analysis was performed to evaluate associations of potential prognostic factors with the rate of successful mobilization. The following factors were analyzed: age, performance status, type of mobilization, diagnosis, number of preceding lines of chemotherapy, preceding radiotherapy, preceding autoHSCT. However, differences for none of the variables were statistically significant (data not shown).

Efficacy of mobilization according to physisian's assessment

Investigators were asked for their subjective opinion regarding the efficacy of plerixafor used for stem cell mobilization. Most physicians stated that it enabled either a single or tandem transplantation. According to 25% of investigators plerixafor shortened the apheresis procedure and according to 23% of physicians it allowed diminishing intensity of chemotherapy (Tab. V).

Toxicity and supportive care

Twenty-two adverse events (AE) were reported in 12 patients according to World Health Organization (WHO) Toxicity Grading Scale. There were 7 AEs of grade 3-4, however, none of them was assessed to be associated with administration of plerixafor. Ten AEs were evaluated as related to plerixafor, most frequently diarrhoea (n = 3), abominal pain (n = 2) and muscular pain (n = 2) (Tab. VI).

Discussion

This is the first prospective multicenter observational study to summarize experience on stem cells mobilization procedures for patients with NHL/HL/MM referred for autoHSCT in Polish hematology centers. The aim of this study was to assess successful collection rate of hematopoietic stem cell (HSC) mobilization with the use of plerixafor in current or proven poor mobilizers, in daily clinical practice.

In many studies, clinical benefits of engraftment rate and overall survival have been analyzed and point toward a correlation between higher $CD34^+$ cell dose and faster engraftment and platelet recovery [4, 6, 7]. The search for an optimal mobilization regimen and efficient collection even in very poor mobilizers was a subject of series of

Table IV. Effect of the use of plerixafor on the number of circulating CD34⁺ cells

	Baseline number of circulating CD34⁺ cells/μL			
	Any	< 5	5 < 10	≥ 10
N	81	43	8	30
CD34⁺ cells/μL before plerixafor (median, range)	4 (0.1-251.9)	1.8 (0.1-4.6)	7.5 (5-9)	45.1 (10-251.9)
CD34⁺ cells/μL after 1st dose of plerixafor (median, range)	25.5 (0.2-708.4)	13.2 (0.2-57)	28.3 (20-75)	68.1 (11-708.4)
Fold increase	3.3 (0.3-155)	6.1 (0.7-155)	4.5 (2.2-8.3)	2.1 (0.3-7.7)

The analysis was restricted to 81 patients with available data.

Table V. Final physician's assessment of mobilization effect (more than one answer possible)

Plerixafor administration:	No of indications
enabled a single transplant	58 (53%)
enabled a tandem transplant	9 (8%)
desired number of CD34⁺ cells was achieved	12 (11%)
shortened apheresis procedure	27 (25%)
gave a foreseeable effect and made it easy to plan apheresis procedure	11 (10%)
it made diminishing of chemotherapy mobilization possible	25 (23%)
other, including inefficacy	15 (14%)

Table VI. Adverse events

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Relation to the use of Plerixafor
Headache	1 (1%)	–	–	–	1 (1%)	Yes
Diarrhoea	2 (2%)	1 (1%)	–	–	3 (3%)	Possible
Abdominal pain	1 (1%)	1 (1%)	–	–	2 (2%)	Possible
Nausea	–	1 (1%)	–	–	1 (%)	Possible
Rash	1 (1%)	–	–	–	1 (%)	Yes
Muscular pain	2 (2%)	–	–	–	2 (2%)	Yes
Haemorrhage	–	–	1 (1%)	–	1 (1%)	No
Cold agglutinin disease	–	–	–	1 (1%)	1 (1%)	No
Infection	–	1 (1%)	–	1 (1%)	2 (2%)	No
Tumor lysis syndrome	–	–	–	1 (1%)	1 (1%)	No
Polyneuropathy	–	1 (1%)	1 (1%)	1 (1%)	3 (3%)	No
Body weight loss	–	–	1 (1%)	–	1 (1%)	No

prospective, randomized clinical trials, reviewed by Sheppard et al. [10]. One way to achieve effective mobilization of hematopoietic cells is to use G-CSF in combination with chemotherapy instead of G-CSF alone. It has been postulated that addition of chemotherapy may contribute to in vivo purging thus reducing the risk of graft contamination with residual malignant cells. This hypothesis, however, has not been confirmed in the clinical setting. Among various protocols reported in the literature, DHAP (dexamethasone, cytarbine, and cisplatin) with or without rituximab is one of the most widely used regimens. It produces a high rate of complete or partial responses in patients with relapsed or refractory HL as well as both indolent and aggressive NHL [25-27]. In the analysis by the PLRG, intermediate-dose cytarabine (ID-AraC) + G-CSF was compared to DHAP + G-CSF for stem cell mobilization in patients with lymphoma. In the ID-AraC group, 96% of patients collected at least 2×10^6 CD34⁺ cells/kg compared with 71% in the DHAP group ($p = 0.0006$) [28]. At the time of that study plerixafor was not available in Poland [28]. The efficacy of ID-AraC as a first or second mobilization was also documented in patients with MM [29, 30]. In the population of poor mobilizers and/or after failure of previous mobilization, administration of plerixafor has been considered as a good and cost-effective alternative to chemotherapy [31, 32]. Addition of plerixafor to G-CSF is useful to achieve efficient collection even in very poor mobilizers as a hope for patients with diminished hematopoietic function [13-17, 19]. Cost-effectiveness of hematopoietic stem cell mobilization strategies including plerixafor in MM and lymphoma patients have been discussed and agreed by many authors [18, 31, 32]. There are several studies regarding the additional cost related to the use of plerixafor under different protocols. These costs depend on local fees and prices as well as the perspective adopted in the cost analysis; however, most studies concluded that the use of plerixafor led to an additional but acceptable cost, given the clinical benefit obtained [31-34]. According to the current practice, the option of in-hospital or home administration for plerixafor injection to poor mobilizers has

no adverse consequences on subsequent hematopoietic stem cell harvest [33].

In our study, despite a heavily pretreated and poorly mobilizing patient population, administration of plerixafor allowed the collection of a sufficient number for stem cells in 55% of patients referred for single autoHSCT and 56% of those planned for double procedure. We were unable to distinguish a subgroup of patients who may be at risk of failure after plerixafor-based mobilization. The effect was comparable regardless of laboratory parameters including the number of circulating $CD34^+$ cells prior to drug administration. In addition, none of the clinical features was associated with the risk of mobilization failure in an univariate analysis. Finally, the therapy was well tolerated with no serious adverse events relative to administration of plerixafor. These findings should be useful to create a national guideline regarding strategies to optimize stem cell mobilization.

Conclusion

Plerixafor treatment is a valuable therapeutic option for NHL, HL, MM patients scheduled for autoHSCT with risk factors for mobilization failure, with minor toxicity and very good efficacy.

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Authors' contributions/Wkład autorów

SG – study desing, data analysis, interpretation of results, writing the manuscript.

SO, JR-J, JD, JM, JS-CH, ASZ, WL, ACZ, MM, MS-W, JD-S, PS, AE, EP-K, TO, MO, ŁT, MT – data collection, interpretation of results, reviewing the manuscript.

Conflict of interest/Konflikt interesu

All authors received honoraria from Sanofi related to the study conduct.

Ethics/Etyka

The work descibed in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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