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Efficacy and safety of stem cell mobilization with cyclophosphamide plus etoposide versus cyclophosphamide alone

Skuteczność oraz bezpieczeństwo mobilizacji komórek macierzystych z wykorzystaniem cyklofosfamidu i etopozydu w porównaniu z samym cyklofosfamidem

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The use of the combination of two cytostatics cyclophosphamide (CTX) and etoposide (VEP) and G-CSF is a reasonable alternative, especially for stem mobilization in multiple myeloma (MM) patients from countries in which newer treatments are limited due to financial constraints.

The aim of this study was to compare the efficacy and safety of CTX-VEP versus CTX alone for mobilization of hematopoietic stem cells in MM patients. The analysis included 48 consecutive MM patients mobilized with CTX-VEP compared to 43 consecutive historical controls mobilized with CTX alone.

The two groups of MM patients did not differ in terms of the median number of apheresis procedures, median yield the first day, median numbers of harvested CD34+ cells, proportion of patients with at least 5 x 10^6/kg yield and incidence of non-hematological complications. The median cumulative dose of G-CSF given to individuals in the CTX-VEP group was significantly lower than in the CTX group (p<0.001). The incidence of post-mobilization thrombocytopenia was higher in the CTX group (p<0.001). The median time to platelet count >20 x 10^9/l (10 vs. 11 days, p=0.004) and the median time to neutrophil count >50 x 10^9/l (11 vs. 13 days, p<0.001) were significantly shorter among the patients mobilized with CTX-VEP than in those treated with CTX alone.

These findings suggest that CTX-VEP is as efficacious and possibly safer than CTX alone.

Wprowadzenie: Zastosowanie połączenia dwóch cytostatyków cyklofosfamidu (CTX) i etopozydu (VEP) wraz z G-CSF jest rozwiązaniem alternatywnym, w szczególności u pacjentów ze szpiczakiem plazmocytowym (MM) z krajów, w których nowe terapie nie są w pełni refundowane.

W pracy porównano skuteczność oraz bezpieczeństwo zastosowania cyklofosfamidu i etopozydu (CTX-VEP) w porównaniu z samym cyklofosfamidem (CTX) przy mobilizacji komórek macierzystych u pacjentów z MM.

Materiał i Metodyka: Analizą objęto 48 chorych z MM gdzie zastosowano protokół CTX-VEP w porównaniu do historycznej kontroli u 43 pacjentów z samym CTX.

Wyniki: Obie grupy nie różniły się pod względem liczby wykonanych procedur aferezy, ilości zebranego materiału przeszczepowego w dniu pierwszym, mediany liczby zebranych komórek CD34+, odsetka pacjentów, którzy uzyskali liczbę komórek co najmniej 5 x 10^6/kg oraz występowania powikłań nie hematologicznych po chemioterapii. Średnia skumulowana dawka G-CSF podana osobom w grupie CTX-VEP była znacząco niższa w porównaniu z grupą CTX (p<0,001). Częstość występowania małopłytkowości po mobilizacji w grupie CTX był wyższy w porównaniu z CTX-VEP (p<0,001). Oceniając medianę czasu do osiągnięcia liczby płytek krwi > 20 x 10^9/l (10 vs 11 dni, p = 0,004) oraz medianę czasu do odnowy neutrofilów > 50 x 10^9/l (11 vs 13 dni, p <0,001) uzyskano istotnie krótsze czasy wśród pacjentów z protokołem CTX-VEP w porównaniu do samego CTX.

Wnioski: Nasze dane sugerują, iż protokół CTX-VEP jest co najmniej tak samo skutecznym sposobem mobilizacji jak CTX ale może być to sposób bezpieczniejszy.

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Introduction

Autologous hematopoietic stem cell transplantation (auto-HSCT) is a standard treatment of multiple myeloma (MM) patients [1]. The main prerequisite of successful engraftment is the number of mobilized peripheral blood stem cells. It is assumed that successful single auto-HSCT

procedure requires minimum 2 x 10^6 CD34+ cells/kg [2-5]. Ideally, a minimum of 5 x 10^6 CD34+ cells/kg should be infused for each transplant. Since MM patients may be candidates for tandem auto-HSCT, the minimum number of stem cells that should be harvested is 5-6 x 10^6/kg with a goal of 10 x 10^6 CD34+ cells/kg [6-8]. Studies have shown that an infusion of >5 x 10^6 CD34+ cells/kg does not result in more rapid engraftment, lower morbidity, decreased demand for transfusions, use of antibiotics, or improved survival [9,10].

Peripheral blood stem cells are usually mobilized with cytokines, predominantly with granulocyte colony stimulating factor (G-CSF). However, the efficacy of the mobilization is greater (fewer collections, higher yields) if the administration of a G-CSF is preceded by the administration of a cytostatic agent [11,12]. The use of such combined mobilization protocols is also justified economically, as it usually results in decreased need for additional leukapheresis procedures [13]. However, application of the combined mobilization protocols may be limited due to toxicity of cytostatic agents including the need for hospitalization transfusions and infectious complications [11]. Cyclophosphamide (CTX), administered at a 1.5-7 g/m^2 is the most commonly used chemotherapeutic agent for stem cell mobilization in MM patients [14-16]. A number of other regimens have been reported such as cyclophosphamide/paclitaxel, cyclophosphamide/dexamethasone/etoposide/cisplatin (CDEP and bortezomib/lenalidomide/dexamethasone/cisplatin/adriamycin/cyclophosphamide/etoposide (VRD-PACE). Chemotherapy plus hematopoietic growth factors can circumvent the difficulty of stem cell mobilization induced by prolonged immunomodulatory agent exposure [17,18]. The list of potential risk factors of mobilization failure includes older age, concomitant thrombocytopenia, and, most of all, the number of lines of previous chemotherapy [19-22].

This stimulated research on potential novel, more efficient albeit still safe, protocols for stem cell mobilization. A widespread application of hematopoietic growth factors alone (e.g. G-CSF with or without CXCR4 antagonist plerixafor) may be limited due to their high cost [23]. The use of the combination of CTX and VEP has been previously documented [17,24,25] and is a reasonable alternative, especially in MM patients from countries in which newer treatments are not limited due to financial constraints (plerixafor). The objective of this study is to compare the efficacy and safety of CTX versus CTX-VEP in patients with MM.

Materials and Methods

Ethics

The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Bioethics Committee at the Jagiellonian University Medical College in Krakow. All the participants gave their written informed consent for participation in the project.

Patients

The retrospective analysis included the data of 48 consecutive MM patients who received mobilization with CTX-VEP at our institution between January 2013 and January 2015. These patients were compared with historical controls: 43 consecutive MM patients mobilized with CTX alone at our institution between March 2005 and November 2012. Only the patients with at least partial response (PR) to systemic therapy underwent mobilization and subsequent auto-HSCT. All the patients were treated at the Clinical Department of Hematology, Krakow University Hospital in Krakow Poland.

Mobilization protocol

In the CTX group, CTX 2-5 g/m^2 was administered intravenously (IV) over 1 hour on day 1, with adequate hydration, urine alkalization and Mesna prophylaxis. In the CTX-VEP group, in addition to CTX (2 g/m^2 on the same schedule), VEP 200 mg/m^2 was administered as a 6-hour IV infusion on day 1. Anti-emetic prophylaxis (ondansetron 12 mg iv plus dexamethasone 10 mg iv) was given routinely irrespective of the mobilization protocol.

G-CSF (filgrastim, 7-10 µg/kg actual body weight subcutaneously) was started on day +5 and continued daily until the last leukapheresis. An anti-infectious prophylaxis (oral ciprofloxacin 500 mg twice daily) was used routinely during the mobilization. Transfusions of a leukocyte-poor and irradiated platelet concentrate were administered for platelet counts below 20 x 10^9/l or below 50 x 10^9/l with active bleeding or need for introduction of the central venous catheter for leukapheresis. Packed red blood cell (RBC) transfusions were administered to maintain hemoglobin concentration ≥8 g/dl. Toxicity was assessed using the Common Terminology Criteria for Adverse Events version 4.0.3.

Leukapheresis

The number of circulating CD34+ cells was evaluated on the first day of neutrophil recovery >1 x 10^9/l by means of immunophenotyping using a BD FACSCanto II flow cytometer (BD Biosciences, San Jose, CA, USA). The leukapheresis was started when the number of circulating CD34+ cells exceeded 20/µl. The manually controlled procedure was performed with a COBE Spectra separator (CaridianBCT Inc, Lakewood CO, USA) in conjunction with auto-PBSC software. At least 15,000 ml of the blood were routinely processed on the separator. The target CD34+ yield was at least 5 × 10^6/kg, i.e. the number sufficient for a tandem auto-HSCT procedure.

Cryopreservation

Collected cells (1:1) were cryopreserved in 10% solution of dimethyl sulfoxide (DMSO) in autologous plasma. Controlled rate freezing was achieved with an IceCube14M freezer (Sy-Lab, Neupurkersdorf, Austria). The rate of cooling was set at -1°C per minute, and temperature fluctuations did not exceed 1-2°C. The cells (target density 1 x 10^5/ml) were packed into 100-ml freezing bags, which were placed in cryo-cassettes and stored in liquid phase nitrogen (ca. -175°C) for 2-12 weeks, i.e. until the auto-HSCT procedure.

Statistical analysis

Normal distribution of continuous variables was verified with the Kolmogorov-Smirnov test. As none of the analyzed variables was distributed normally, their statistical characteristics are presented as medians and ranges, and the intergroup comparisons were conducted with the Man Whitney U-test. Distributions of discrete and qualitative variables in the studied groups were compared with the Pearson's chi-square test and Fisher's exact test. The time-to-neutrophil and time-to-platelet recovery were estimated with the Kaplan-Meier method and the probabilities of the recovery within the groups were compared with the log-rank test. All the tests were two-sided. All the calculations were carried out using Statistica 10 software (StatSoft, Tulsa, OK, USA), with the threshold of statistical significance set at $p \leq 0.05$.

Results

There were no significant differences in patient characteristics between the CTX and CTX-VEP groups except that patients in the CTX-VEP group were significantly older than the CTX alone group (median age: 59.5 vs. 52 years, $p<0.001$) (Table I).

Efficacy of the mobilization

All patients from both groups collected at least 2 x 10^6 CD34+ cells/kg. The median number of apheresis procedures, median yield the first day, median numbers of harvested CD34+ cells, and the proportion of patients with at least 5 x 10^6/kg yield were similar between the two groups. However, the median cumulative dose of G-CSF given to individuals mobilized with CTX-VEP was significantly lower than in those mobilized with CTX alone (Table II).

Toxicity

The incidence of post-mobilization thrombocytopenia in patients mobilized with CTX alone was significantly higher than in individuals treated with CTX-VEP (Table II). Among the 24 episodes of thrombocytopenia recorded in the CTX group, there were seven cases of grade 3 thrombocytopenia, as well as 3 and 14 cases of grade 2 and 1 thrombocytopenia, respectively. In turn, no grade 3 thrombocytopenia was seen, and two cases of grade 1 and 2 thrombocytopenia were documented in patients mobilized with CTX-VEP.

The two groups did not differ significantly in terms of the incidence of non-hematological complications (Tab. II). The list of non-hematological morbidities recorded in patients mobilized with CTX-VEP included eye swelling, diarrhea and thrombosis at a site of central catheter insertion, as well as single case of one-day fever. In turn, two opportunistic infections, both corresponding to grade 2 toxicity, were documented in individuals subjected to mobilization with CTX alone.

Recovery of the hematopoietic system after auto-HSCT

Forty two (98%) patients treated with CTX alone and 41 (85%) persons treated with CTX-VEP proceeded to auto-HSCT

Table I

Demographic and clinical characteristics of the study participants.

Demograficzna i kliniczna charakterystyka uczestników badania.

Parameter	CTX (n=43)	CTX-VEP (n=48)	p-value
Median age, years	52 (34-66)	59.5 (44-76)	<0.001
Sex:			
- male	28 (65%)	23 (48%)	0.139
- female	15 (35%)	25 (52%)	
Disease phase:			
- CR	16 (37%)	14 (29%)	0.090
- VGPR	8 (19%)	19 (40%)	
- PR	19 (44%)	15 (31%)	
Median interval diagnosis-mobilization (months)	7 (2-55)	5.5 (1-98)	0.237
Type of MM:			
- IgG	22 (56%)	32 (71%)	0.132
- IgA	11 (28%)	5 (11%)	
- kappa	1 (3%)	4 (9%)	
- lambda	5 (13%)	4 (9%)	
- non-secretory	4 (9%)	3 (6%)	
ISS stage:			
- I	12 (28%)	17 (35%)	0.136
- II	8 (19%)	15 (31%)	
- III	23 (53%)	16 (33%)	
Lines of preceding chemotherapy:			
- 1	32 (76%)	38 (79%)	0.504
- 2	9 (22%)	7 (15%)	
- 3 or more	1 (3%)	3 (6%)	
Median number of preceding chemotherapy cycles	**5 (3-8)**	**5 (3-28)**	**0.833**

Abbreviation: CTX = cyclophosphamide; CTX-VEP = cyclophosphamide + etoposide; CR = complete response; PR = partial response; VGPR = very good partial response; MM = multiple myeloma; ISS = International Staging System.

Table II

Efficacy and safety of peripheral blood CD34+ cell mobilization with cyclophosphamide alone (CTX) or cyclophosphamide + etoposide (CTX-VEP).

Skuteczność oraz bezpieczeństwo mobilizacji komórek CD34+ z użyciem samego cyklofosfamidu (CTX) oraz połączenia cyklofosfamidu z etopozydem (CTX-VEP).

Parameter	CTX (n=43)	CTX-VEP (n=48)	p-value
Median number of apheresis procedures	2 (1-2)	2 (1-2)	0.581
Median CD34+ yield the first day (x 10^6/kg)	4.04 (1.50-47.12)	4.90 (1.17-23.74)	0.309
Median level of collected CD34+ (x 10^6/kg)	6.67 (2.39-47.12)	7.43 (2.25-23.74)	0.402
≥5 x 10^6/kg collected CD34+ cells	35 (81%)	33 (69%)	0.228
Median cumulative G-CSF dose (μg)	5760 (3360-9600)	4320 (2880-7200)	<0.001
Thrombocytopenia at mobilization	24 (56%)	2 (4%)	<0.001
Platelet transfusion	1 (2%)	0 (0%)	0.442
Erythrocyte transfusion	5 (12%)	3 (6%)	0.457
Non-hematological complications	2 (5%)	4 (8%)	0.649
Median time to neutrophil recovery	13 (10-17)	11 (10-14)	<0.001
Median time to platelet recovery	11 (11-19)	10 (8-14)	0.004

Abbreviation: CTX = cyclophosphamide; CTX-VEP = cyclophosphamide + etoposide; G-CSF = granulocyte colony stimulating factor.

directly after the mobilization. In the remaining patients, the procedure was cancelled or postponed due to post-mobilization progression of disease.

The median time to platelet recovery >20 x 10^9/L (10 [range 8-14] vs. 11 [11-19] days, p=0.004; (Figure 1) and the median time to neutrophil recovery >0.5 x 10^9/L (11 [10-14] vs. 13 [10-17] days, p<0.001; (Figure 2) was significantly shorter in CTX-VEP group than in the CTX alone group.

Discussion

The identification of an optimal regimen of mobilization that could be used in patients with hematological malignancies has been subject of several prospective studies [26]. However, these studies did not show unequivocally, which of the mobilization regimens is the most efficient, still retaining an acceptable safety profile [27]. Consequently, it is generally postulated that mobilized regimens should be personalized on the basis of an individual risk profile of mobilization failure (e.g. disease type and status, number of transplants, comorbidities, prior lines), and taking into account economic conditions and limitations [26]. Further, more stem cells are required in MM patients who are candidates for a tandem auto-HSCT procedure [28]. Moreover, according to some authors, chemomobilization may reduce the clonogenic potential of cells present in the graft [6,14,29,30]. The CXCR4 inhibitor, plerixafor, is also an effective hematopoietic stem cell mobilizer, but economic considerations limit its use in many countries.

In previous studies of MM patients, the administration of G-CSF at various doses and schedules usually followed CTX administration [26]. These mobilization regimens are associated with significantly higher CD34+ yield than administration of a G-CSF alone [11]. However, the efficacy of mobilization with CTX increases proportionally to its dose, which is associated with greater toxicity [31]. This observation stimulated research on developing a less toxic mobilization regimen whose efficacy would be similar to CTX. Several previous studies evaluated the efficacy and safety of CTX-VEP for stem cell mobilization in MM patients [17,24, 25]. In our study, this regimen was equally efficient as CTX alone in terms of both the absolute CD34+ yield and the percentage of patients achieving their target goal (≥5 x 10^6 CD34+ cells/kg). However, our mobilization yields were slightly lower than reported by others with this regimen: up to 22.39 x 10^6 CD34+ cells/kg and >90% of responders [17,25] compared to our yield of 7.43 x 10^6 cells/kg and 69% of adequate stem cell collections. These differences may be related to the fact that our study was a retrospective analysis, and thus some of our patients were more heavily pre-treated and only individuals with responsive disease were mobilized. Further, the CTX-VEP was an older population, and older age is a risk factor of mobilization failure [19-22]. Consequently, it cannot be excluded that our analysis would show that CTX-VEP is superior to CTX alone, if conducted in a prospective manner with matching the analyzed groups for the risk of mobilization failure.

Nevertheless, the present retrospective analysis provides data suggesting the superiority of CTX-VEP mobilization protocol. Firstly, the use of this regimen was associated with lower incidence of hematological morbidities, especially thrombocytopenia, suggesting that CTX-VEP is safer than CTX alone at a comparable efficacy. Greater safety (and also higher cost-effectiveness) of CTX-VEP was also supported by the fact that patients mobilized with these agents required significantly lower cumulative doses of

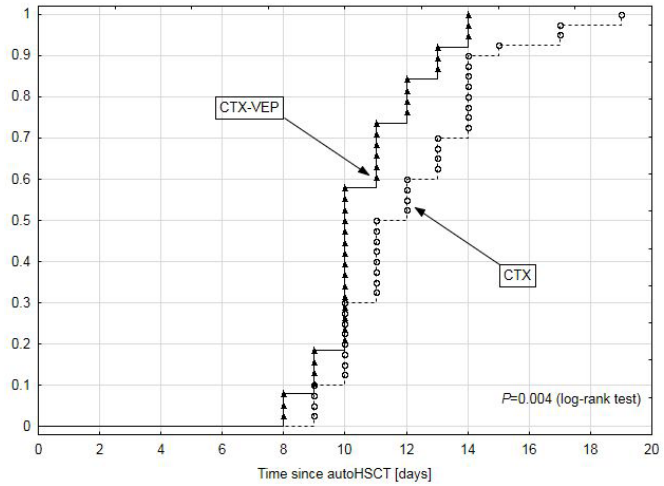

Figure 1

Recovery of Platelet > 20 x 10^9/l after auto-HSCT according to type of mobilization regimen. Only patients who proceeded to auto-HSCT were analyzed.

Odbudowa płytek krwi > 20 x 10^9/l po procedurze auto-HSCT w zależności od sposobu mobilizacji. Tylko pacjenci którzy przeszli procedurę auto-HSCT byli ujęci analizą, 42 chorych było mobilizowanych przy pomocy cyklofosfamidu (CTX) i 41 chorych z użyciem cyklofosfamidu i etopozydu (CTX-VEP).

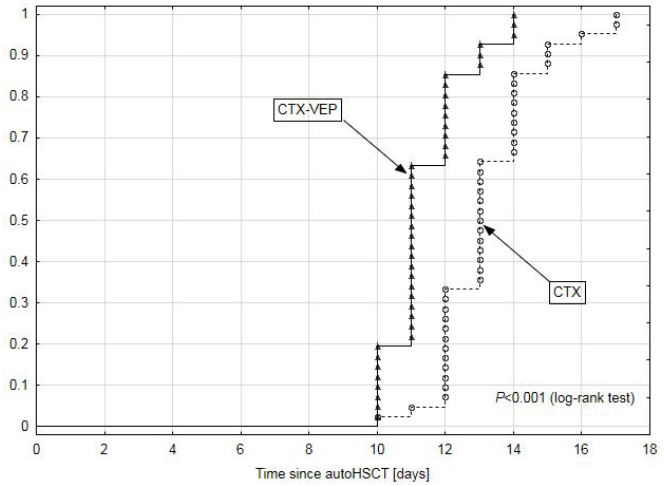

Figure 2

Recovery of Neutrophil > 500 x 10^9/l after auto-HSCT according to type of mobilization regimen. Only patients who proceeded to auto-HSCT were analyzed.

Odbudowa neutrofili > 500 x 10^9/l po procedurze auto-HSCT w zależności od sposobu mobilizacji. Tylko pacjenci którzy przeszli procedurę auto-HSCT byli ujęci analizą, 42 chorych było mobilizowanych przy pomocy cyklofosfamidu (CTX) i 41 chorych z użyciem cyklofosfamidu i etopozydu (CTX-VEP).

G-CSF to obtain a comparable CD34+ yield and fewer blood products. This finding can be interpreted both in terms of the lower risk of potential adverse effects of G-CSF and in the context of lower treatment costs. Moreover, it should be acknowledged that that the efficacy of mobilization is primarily assessed on the basis of engraftment outcomes, rather than solely in terms of the CD34+ yield. In this context, CTX-VEP engraftment kinetics were superior to CTX alone.

When interpreting the results of this study, one should also consider its potential limitations. This is a retrospective analysis and resultant potential selection bias. Moreover, since it was a single-center study, we were unable to collect sufficiently large group of patients providing adequate power of statistical analyses.

Conclusions

Taking into account the potential limitations mentioned above, our findings suggest that CTX-VEP has comparable efficacy with lower hematologic and non-hematologic toxicities compared CTX alone. Given the comparable yields and lower morbidity, CTX-VEP represents a good mobilization option, especially in many cases in which newer mobilization agents cannot be administered due to budgetary limitations.

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