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ORIGINAL ARTICLE

Cost analysis of a randomized stem cell mobilization study in multiple myeloma

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Abstract Upfront autologous stem cell transplantation (ASCT) is the standard therapy for younger multiple myeloma (MM) patients. MM patients usually undergo stem cell mobilization with cyclophosphamide (CY) followed by granulocyte colony-stimulating factor (G-CSF), or with G-CSF alone. A limited number of randomized studies are available comparing costs of different mobilization strategies. Eighty transplant-eligible patients aged up to 70 years with untreated MM were included in this prospective study. The patients were treated with RVD induction for three 21-day cycles and randomized 1:1 at inclusion into one of the two mobilization arms CY 2 g/m^2 + G-CSF [arm A] vs. G-CSF alone [arm B]. Plerixafor was given according to a specific algorithm if needed. Sixty-nine patients who received mobilization followed by blood graft collection were included in the cost analysis. The median total costs of the mobilization phase were significantly higher in arm A than in arm B (3855 € vs. 772 €, $p \leq 0.001$). The cumulative median cost of the mobilization and collection phases was significantly lower in arm B than in arm A (8524 € vs. 11,622 €, $p = 0.012$). There was no significant difference between the arms in the total median costs of ASCT ($n = 59$) (34,997 € in arm A vs. 31,981 € in arm B, $p = 0.118$). Mobilization with G-CSF alone seems to be a preferable mobilization method for MM patients in terms of mobilization and apheresis costs. In addition, it requires less hospital resource utilization.

Keywords Stem cell mobilization · Autologous stem cell transplantation · Multiple myeloma · Cost analysis · Cyclophosphamide · Plerixafor

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Introduction

Autologous stem cell transplantation (ASCT) is a standard therapy in symptomatic younger multiple myeloma (MM) patients [1, 2]. ASCT has been shown to improve overall survival (OS), event-free survival (EFS), and complete remission (CR) rates when compared with standard therapy [3, 4]. Currently, upfront ASCT is recommended for all transplant-eligible patients, in spite of the introduction of novel myeloma drugs (e.g., proteasome inhibitors and immunomodulatory drugs) [5]. In addition, ASCT has been shown to be an effective treatment strategy for relapsed disease, even for patients with prior ASCT [6, 7]. Because almost all ASCTs in adults are performed using blood stem cell grafts [8], successful stem cell mobilization and collection are prerequisites for ASCT. However, the optimal mobilization regimen is still under

debate and mobilization strategies differ between various centers and countries.

Traditionally, stem cell mobilization in myeloma patients has been achieved with high-dose cyclophosphamide (CY) (4–7 g/m^2) followed by granulocyte colony-stimulating factor (G-CSF) [9, 10]. More recently, lower doses of CY (1.5–2 g/m^2) combined with G-CSF have been used [11, 12]. However, due to the toxicity of cyclophosphamide, mobilization with G-CSF alone has become a preferred method for stem cellmobilization in many transplantation centers [13, 14]. This concept has been supported by recent studies showing that the use of cyclophosphamide-based mobilization does not have an impact on disease control or survival after ASCT [15–17].

Stem cell mobilization with G-CSF alone has become a more feasible option because of the introduction of plerixafor (CXCR4 antagonist, Mozobil®). The superiority of G-CSF plus plerixafor over G-CSF alone has been shown in a phase III study [18]. While plerixafor is generally well tolerated and is associated with a robust stem cell mobilization, cost is the major factor limiting its use. The official hospital price for a single 24 mg plerixafor dose in Finland is 6250 €. Many algorithms to rationalize plerixafor use have been published [19, 20]. However, there are only a few algorithms based on prospective data and/or prospective validation with cost-effectiveness analysis [21].

As a part of a mobilization substudy of the Finnish Myeloma Study Group-MM02 prospective phase II trial (#NCT01790737), we have evaluated the costs of different phases (mobilization, stem cell collection, high-dose therapy, and early post-transplant) of ASCT in MM patients who underwent mobilization with low-dose CY plus G-CSF vs. with G-CSF alone after lenalidomide-based induction (lenalidomide, bortezomib, and dexamethasone, RVD).

Patients and methods

Patients

Eighty transplant-eligible patients aged up to 70 years with untreated MM were included in this prospective phase II study. The main exclusion criteria were peripheral neuropathy grade ≥2, significant liver dysfunction, severe cardiac dysfunction, severe renal failure (glomerular filtration rate <15 ml/min, unless in hemodialysis) and contraindication for the use of thromboprophylaxis or a history of active malignancy during the past 5 years [22].

Sixty-nine patients (34 patients in arm A and 35 patients in arm B) from whom CD34$^+$ cells were successfully collected were included in this cost analysis. Eleven patients (14 %) were dropped out before mobilization therapy due to toxicity ($n = 9$) or early progression ($n = 2$). Of the collected patients, 10 (14 %) patients who underwent mobilization did not proceed to autologous transplantation due to progressive disease ($n = 6$), allogeneic transplantation ($n = 3$), or severe comorbidities ($n = 1$). There were no mobilization failures. The patient characteristics of the mobilization study are presented in Table 1. There were no significant differences between the groups in terms of median levels of hemoglobin, leukocyte, platelet, albumin, creatinine, or β_2-microglobulin prior to mobilization therapy or high-dose treatment and ASCT (data not shown).

Treatment and mobilization

The patients were randomized (1:1) at inclusion into one of the two mobilization arms and treated with RVD induction for three 21-day cycles [22]. The mobilization in arm A was CY 2 g/m^2 on d + 1 plus filgrastim 5 μg/kg/day starting on d + 4 and in arm B, filgrastim 10 μg/kg/day alone starting on d + 1. In arm A, patients were hospitalized for CY and mesna infusions and the median length of stay was 3 days. Plerixafor was given subcutaneously with a dose of 240 μg/kg if the B-CD34$^+$ level was $<10 \times 10^6$/L in either arm provided that the white blood cell count was at least 10×10^9/L in arm A or d + 5 has been achieved in arm B. Plerixafor was also given if the yield of the first apheresis was $<1 \times 10^6$/kg CD34$^+$ cells. If plerixafor was started, it was continued until the predetermined number of CD34$^+$ cells were collected. Apheresis was initiated if the blood CD34$^+$ cell level was $>10 \times 10^6$/L on d + 10 or on d + 5 in arms A and B, respectively. The collection target was defined beforehand ($\geq 3 \times 10^6$/kg CD34$^+$ cells for a single transplant or $\geq 6 \times 10^6$/kg if two transplants were an option). High-dose melphalan (200 mg/m^2) was used as high-dose therapy and G-CSF was recommended after the graft infusion starting on d + 5 if the number of collected CD34$^+$ cells was $<3 \times 10^6$/kg [22].

Financial analysis

The costs per inpatient day were collected from all participating transplantation units (five university hospitals in Finland). The costs of routine treatments (e.g., antibiotics, intravenous fluids) and procedures (e.g., mandatory laboratory tests) during hospital stays were included in the costs of the inpatient day. Because there were some differences between the hospitals, the average values of the costs were calculated and were used in the cost calculations. The prices of medications were acquired from the Hospital Pharmacy of Kuopio University Hospital, Kuopio, Finland, and these prices were used for all patients because prices are generally the same in all Finnish hospitals. All blood products were supplied by The Finnish Red Cross Blood Service, and the prices of the products used were as published on their Web site. Unscheduled hospital stays (e.g., due to adverse events of mobilization therapy)

Table 1 Patient characteristics

Variable	Arm A (CY + G-CSF), $n = 34$	Arm B (G-CSF), $n = 35$	Significance p
Sex, *n* (%)			1.000
Men	18 (53 %)	19 (54 %)	
Women	16 (47 %)	16 (46 %)	
Age (years)			0.828
Median (range)	62 (48–69)	62 (40–70)	
Weight (kg)			0.674
Median (range)	76 (48–108)	74 (51–117)	
ISS, *n* (%)			0.438
I	6 (17 %)	13 (37 %)	
II	23 (68 %)	15 (43 %)	
III	5 (15 %)	7 (20 %)	
IMWG risk, *n* (%)			0.160
Low	5 (15 %)	3 (9 %)	
Standard	26 (76 %)	25 (71 %)	
High	3 (9 %)	7 (20 %)	
Disease status, prior to mobilization, *n* (%)			0.645
VGPR or better	20 (59 %)	18 (51 %)	
PR	12 (35 %)	16 (46 %)	
SD	1 (3 %)	–	
PD	1 (3 %)	1 (3 %)	
Collection target			0.469
For single transplantation ($\geq 3 \times 10^6$/kg $CD34^+$ cells)	13 (38 %)	17 (49 %)	
For two transplantations ($\geq 6 \times 10^6$/kg $CD34^+$ cells)	21 (62 %)	18 (51 %)	

CY cyclophosphamide, *G-CSF* granulocyte colony-stimulating factor, *ISS* International Staging System, *IMWG* International Myeloma Working Group, *VGPR* very good partial response, *PR* partial response, *SD* stable disease, *PD* progressive disease

were noted in the calculations when present. The costs of high-dose treatment and early post-transplant phase were calculated for transplanted patients. The estimated average costs used in the calculations are presented in Table 2.

Statistics

All calculations and statistical analyses were conducted using IBM SPSS Statistics 23.0 for Windows (IBM Corp., Armonk, NY, USA). Due to a low number of observations, Fisher's exact test, the Mann–Whitney *U* test, and Pearson's chi-squared test were used to analyze the data. Continuous variables are presented as medians with ranges and categorical variables in percentages. A two-tailed p value of less than 0.05 was considered statistically significant.

Ethics

The Research Ethics Committee of the Northern Savo Hospital District approved the study protocol, and it was conducted according to the Declaration of Helsinki, International Conference of Harmonization and Guidelines for Good Clinical Practice. Written informed consent was obtained from

Table 2 Estimated average costs

Phase/cost	Amount/price €
General costs	
Inpatient/hospital day (incl. routine treatments)	1000
Platelets ("single unit/bag")	454
Red blood cells ("single unit/bag")	142
Mobilization phase	
Cyclophosphamide (2 g/m^2) + mesna	195
G-CSF	
• 30 MU (outpatient/inpatient)	70/11
• 48 MU (outpatient/inpatient)	110/15
Plerixafor (Mozobil®) 24 mg	6250
Collection phase	
Measurement of circulating $CD34^+$ cells	150
Apheresis (incl. all material and laboratory costs)	2226

G-CSF granulocyte colony-stimulating factor, *MU* million units

all patients before inclusion. The Finnish Myeloma Study Group-MM02 trial was approved by the Finnish Medicines Agency and registered at www.clinicaltrials.gov as #NCT01790737.

Results

The median number of aphereses was two (range 1–3 in arm A and 1–4 in arm B) in both arms ($p = 0.273$). The proportion of patients reaching the predetermined number of $CD34^+$ cells with one to two aphereses was 62 % in arm A and 50 % in arm B ($p = 0.662$). All patients in both arms reached a yield of $\geq 2 \times 10^6$/kg $CD34^+$ cells with ≤3 aphereses. The total stem cell yield was 6.7×10^6/kg $CD34^+$ cells (range 2.2–12.4 × 10^6/kg) in arm A and 5.3×10^6/kg $CD34^+$ cells (2.4–12.4 × 10^6/kg) in arm B ($p = 0.012$). The median number of the stem cell storage bags was significantly lower ($p = 0.013$) in arm A than in arm B (4; range 2–8 vs. 5; 2–12). The detailed results of a mobilization substudy of the Finnish Myeloma Study Group-MM02 trial have been presented elsewhere [22].

The median total costs of the mobilization phase were significantly higher ($p \leq 0.001$) in arm A than in arm B (3855 €; range 2615 €–16,400 € vs. 772 €; 560 €–13,126 €). This was mostly due to the hospital treatment period needed for cyclophosphamide mobilization. The median costs of G-CSF were significantly higher ($p \leq 0.001$) in arm B than in arm A (747 €; 560 €–1000 € vs. 660 €; 420 €–960 €). There were four (12 %) hospital treatment periods due to fever in arm A after mobilization therapy vs. one (3 %) in arm B ($p = 0.169$).

The median total costs of the collection phase were 7752 € (range 3376 €–13,376 € [arm A], 3376 €–14,504 € [arm B]) in both arms ($p = 0.814$). The cumulative median costs of the mobilization and the collection phases of all patients was 11,622 € (5991 €–28,678 €) in arm A and 8524 € (3936 €–27,630 €) in arm B ($p = 0.012$). Among the patients requiring only one or two aphereses, the cumulative median costs of the mobilization and the collection phases were significantly lower in arm B than in arm A (5316 €; 3936 €–12,186 € vs. 8694 €; 5991 €–16,991 €, $p \leq 0.001$) and (8524 €; 7498 €–14,584 € vs. 12,620 €; 10,378 €–26,617 €, $p \leq 0.001$), respectively. In this patient group, three patients (6 %) were treated with plerixafor. There was no significant difference in the cumulative median costs of the mobilization, and the collection phases in patients requiring three or more aphereses as the median cost was 15,013 € (13,765 €–28,678 €) in arm A and 14,097 € (10,900 €–27,630 €) in arm B ($p = 0.460$). Altogether, seven patients (10 %) (two patients in arm A and five patients in arm B, $p = 0.428$) were treated with plerixafor. Only two patients (3 %, a single patient in both arms) were treated with plerixafor before the initiation of apheresis. Five patients (7 %) were treated with plerixafor before the second ($n = 4$, 6 %) and/or third ($n = 4$, 6 %) apheresis sessions. In addition, a single patient (1 %) received plerixafor before the fourth apheresis session. Of note, 22 % of all patients (13 % in arm A and 30 % in arm B) requiring three or more aphereses were treated with plerixafor ($p = 0.588$). Among the patients with the same predefined collection target, the cumulative median costs of the mobilization and the collection phases were comparable between the arms (for single transplantation, arm A 8991 €; 5991 €–16,991 € vs. arm B 8494 €; 3936 €–14,585 €, $p = 0.103$ and for two transplantations, 13,622 €; 7231 €–28,678 € vs. 8980 €; 3936 €–27,630 €, respectively, $p = 0.140$).

The median cost of high-dose therapy and the early post-transplant phase was 22,829 € (16,340 €–77,585 €) in arm A and 22,183 € (15,829 €–30,375 €) in arm B ($p = 0.785$). The total median cost of stem cell mobilization, collection, and transplantation was 34,997 € (23,366 €–82,366 €) and 31,981 € (22,871 €–53,067 €) in arms A and B, respectively ($p = 0.118$). The detailed costs of different phases are presented in Table 3.

Discussion

The vast majority of all studies concerning cost-effectiveness of different mobilization strategies have been retrospective [23–29]. Although many of these studies investigate well-matched historical cohorts, their retrospective design without randomization makes generalization of their results difficult. In addition, because the majority of published pharmacoeconomic studies are from the USA and healthcare systems vary greatly from country to country, the results cannot be directly generalized to other countries.

The most comprehensive prospective data available are from an interim analysis of an Italian study by Milone et al. The recruited MM patients were compared with a bias-adjusted, historical control group. All patients underwent mobilization with chemomobilization + G-CSF, and plerixafor was given according to a specific algorithm ("on-demand"). The main finding of the cost-effectiveness analysis in this study was that the on-demand strategy did not result in an increase in overall costs [21]. In another prospective study from the UK (the PHANTASTIC trial), the routine use of plerixafor with G-CSF mobilization therapy resulted in an average cost increase of £5245 per MM patient [30]. In our study, mobilization with G-CSF combined with preemptively administered plerixafor resulted in significantly lower total costs of mobilization and collection in patients requiring only one or two aphereses when compared with mobilization with CY + G-CSF. Thus, G-CSF alone seems to be a preferable and adequate method for stem cell mobilization in the majority of MM patients. Because mobilization

Table 3 Median costs

Phase/cost median	Arm A (CY + G-CSF), (€)	Arm B (G-CSF), (€)	Significance *p*
Mobilization phase ($n = 69$)			
CY (2 g/m^2) + mesna (Uromitexan®)	195	0	<0.001
G-CSF	660	747	<0.001
Plerixafor (Mozobil®)	0	0	0.281
Treatment period (hospital days)	3000	0	<0.001
Total (mobilization)	3855	772	<0.001
Collection phase ($n = 69$)			
Measurements of circulating CD34$^+$ cells	300	300	0.925
Aphereses	4452	4452	0.273
Treatment period (hospital days)	3000	3000	0.228
Total (collection)	7752	7752	0.814
High-dose treatment and early post-transplant phase ($n = 59$)			
Melphalan	1375	1375	1.000
Red cell transfusions	0	0	0.300
Platelet transfusions	908	908	0.722
Post-transplant G-CSF	0	0	0.431
Treatment period (hospital days)	21,000	19,500	0.795
Total (high-dose treatment and early post-transplant)	22,829	22,183	0.785
Total costs ($n = 59$)	34,997	31,981	0.118

CY cyclophosphamide, *G-CSF* granulocyte colony-stimulating factor

with CY + G-CSF usually results in a higher stem cell yield, it might be justified for MM patients who are in a high-risk group for poor mobilization. Stratification of mobilization therapy by clinical characteristics that are identifiable before initiation of mobilization, however, has been reported to be problematic [31]. It might also be useful when stem cells are collected for multiple transplantations or when the collection target is set high for any reason. In the consensus guidelines mobilization with G-CSF alone is categorized as an option for first-line mobilization for MM patients, but it should be limited to patients with no more than one previous line of therapy, not previously treated with melphalan or >4 cycles of lenalidomide [19]. Preemptive plerixafor may be used in patients with inadequate mobilization.

We have previously reported on changes in CD34$^+$ stem cell subclasses and lymphocyte subsets of grafts after different mobilization therapies in myeloma patients [32]. These preliminary observations have been confirmed in a recent substudy of the Finnish Myeloma Study Group-MM02 trial [33]. In that study, patients mobilized with G-CSF had a greater proportion of primitive stem cells and much higher numbers of lymphocytes and natural killer cells in their grafts compared with the grafts of patients mobilized with CY + G-CSF. Whether these changes in the graft composition have an impact on progression-free survival or overall survival after ASCT is still an open question and longer follow-up is necessary to address it.

In this study, the median number of the stem cell storage bags was significantly higher among patients mobilized with G-CSF alone. This is probably due to fact that CD34$^+$ cell/mononuclear cell (MNC) ratio is lower in G-CSF mobilized apheresis products. As the grafts are stored at standard cell concentrations, this leads to a higher number of storage bags. It is notable that the Finnish Myeloma Study Group-MM02 study protocol did not include standardization of graft preservation. It is therefore possible that there might have been differences in stem cell storage concentration between the participating transplantation centers. The difference between mobilization methods in the number of the stem cell storage bags, however, was small and its possible impact on the total costs is likely to be only modest. The number of plerixafor-treated patients in this study was too low for any statistical subanalysis on this matter but the use of plerixafor with G-CSF mobilization have been reported to result in a greater number of storage bags [34].

In conclusion, mobilization with G-CSF results in lower total costs of mobilization and collection than mobilization with CY + G-CSF in patients requiring only one or two aphereses. In patients requiring three or more aphereses, there were no significant differences in the costs of the two mobilization approaches. The total costs of ASCT were comparable

between the arms. Because there are no data available from prospective studies regarding stratification of mobilization therapy for different risk groups, such as patients with high risk of poor mobilization or early disease progression after ASCT, future studies including also cost-effectiveness analyses concerning these aspects are warranted to improve selection of an optimal mobilization therapy for individual patients.

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Compliance with ethical standards

Conflict of interest VV has received consultancy fees from Roche, Celgene, Amgen, and Sanofi. RS has received a research grant from Celgene and Janssen, honoraria from Celgene, Janssen, and Sanofi. KR has participated in the Medical Advisory Board organized by Amgen and Takeda and has received consultancy fees from Amgen, Celgene, Roche, and Takeda. EJ has received honoraria from Genzyme, Amgen, and Sanofi and has participated in an EU Leadership meeting organized by Genzyme as well as a Medical Advisory Board meeting organized by Amgen and Takeda. The other authors have no conflicts of interest to disclose.

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