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VTD in comparison with VCD does not affect stem cell yields with G-CSF only mobilization

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Abstract

Triplet induction regimens are standard of care for newly diagnosed transplant eligible multiple myeloma patients. The combinations of bortezomib and dexamethasone with either cyclophosphamide (VCD) or thalidomide (VTD) are widely used. There are no data available on the impact of the two regimens on stem cell harvest by using G-CSF only mobilization. In this study, we retrospectively analyzed data from our national registry. The outcome measures were mobilization failure, CD34+ cell counts on collection day, number of apheresis procedures, and the number of collected cells. Overall, 72 patients were treated with either VCD or VTD. The mobilization failure rates were 7% and 9% ($p = 0.771$) and the total number of collected stem cells were 7.0×10^6 and 6.7×10^6 per kg body weight ($p = 0.710$) for VCD and VTD, respectively. We found no statistically significant difference between the treatment groups in the outcome measures. The addition of thalidomide to bortezomib and dexamethasone (VTD) does not adversely affect stem cell harvest in patients mobilized with G-CSF only.

Keywords:
myeloma, HSCT, stem cell transplantation, mobilization, G-CSF

Introduction

Multiple myeloma (MM) is a hematologic disease characterized by the accumulation of malignant plasma cells in the bone marrow. Triplet induction regimens incorporating novel agents have shown to improve response and prolong progression free survival (PFS) and even overall survival (OS) [1, 2]. Autologous hematopoietic stem cell transplantation (aHSCT), performed in first remission or at relapse, is standard of care for younger fit patients [3, 4, 5]. Successful mobilization and collection of peripheral blood stem cells (PBSC) are required before aHSCT. A target dose of 2×10^6 PBSC per kg body weight is considered a minimum for timely hematopoietic reconstitution, although a higher dose, 3 to 5×10^6 PBSC per kg body weight, is thought to be optimal for earlier engraftment [6, 7, 8]. A second aHSCT can be performed within 6 months (tandem transplant) or following progression. Therefore, an attempt to collect PBSC for at least two aHSCT should be considered. Mobilization with chemotherapy (e.g., intermediate doses of cyclophosphamide) and granulocyte-colony stimulating factor (G-CSF) is standard in most transplant centers and provides higher stem cell yields in fewer apheresis procedures at the cost of increased toxicity and less predictable onset date of apheresis in comparison with G-CSF mobilization only [9, 10]. On the other hand, G-CSF only mobilization fails to achieve the target doses of PBSC in 5–30% of patients [8, 11, 12, 13].

Known factors affecting stem cell mobilization are age, advanced disease status, extensive treatment, thrombocytopenia, prior exposure to irradiation, and alkylating agents [10]. Novel induction regimens using proteasome inhibitors (PI) and especially immunomodulatory drugs (IMIDs) might impact the ability to mobilize and harvest stem cells [14, 15]. In case of lenalidomide, a second generation IMID, there are data supporting its adverse impact on mobilization after prolonged treatment. However, there is no clear evidence of bortezomib impact on stem cell harvest [8, 10]. In the IFM 2005/01 trial comparing bortezomib and dexamethasone (VD) with vincristin, adriamycin, and dexamethasone (VAD), a trend to lower stem cells yields was observed in patients receiving bortezomib [12, 16]. G-CSF alone mobilization was used in this trial. On the contrary, in the HOVON-65/GMMG-HD4 trial comparing bortezomib, adriamycin, dexamethasone (PAD) with VAD, all patients successfully collected stem cells for aHSCT and no impact of bortezomib on collection was observed [17, 18]. Of note, chemomobilization with cyclophosphamide and adriamycin was used as the mobilization procedure. There are limited and contradictory data on the impact of thalidomide on PBSC mobilization and collection, but the impact appears to be small [15, 19, 20]. In addition, the use of G-CSF mobilization alone is a predisposing factor for mobilization failure [11, 14, 15].

Triplet induction regimens incorporating bortezomib, thalidomide, and dexamethasone (VTD) or bortezomib, cyclophosphamide and dexamethasone (VCD) are current standards of care. The available data show a benefit of VTD compared with VCD but at the expense of a higher prevalence of polyneuropathy [4, 5, 21]. There are limited data available for the two regimens on stem cell mobilization efficacy, especially considering the potential negative impact of thalidomide. Owing to feasibility and safety reasons, we use G-CSF only

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mobilization in MM patients at our institution, with chemomobilization and plerixafor reserved for mobilization failures. We undertook a retrospective analysis of our registry data regarding the impact of VTD and VCD induction on stem cell mobilization with G-CSF alone.

Patients and methods

We retrospectively analyzed data from our national registry from the January 1, 2014 to December 31, 2017. All patients gave written consent for registry data collection. A total of 72 consecutive patients with newly diagnosed MM who received first-line induction treatment with VTD or VCD and underwent stem cell mobilization with G-CSF were included. Patients receiving additional treatment or patients with relapsed/refractory disease were not included. VTD treatment consisted of 3 week cycles of bortezomib 1.3 mg/m^2 subcutaneous on days 1, 4, 8, and 11, thalidomide 100 mg daily and dexamethasone 40 mg on days 1–4 of the first cycle and once per week thereafter. VCD treatment incorporated bortezomib and dexamethasone in the same schedule as for VTD plus cyclophosphamide 500 mg/m^2 on day 1, 8, and 15. Following 3–4 cycles of induction treatment, stem cells were mobilized using subcutaneous filgrastim 10 mcg/kg rounded to the nearest available dose for 5 consecutive days. Circulating CD34+ cells were determined in peripheral blood on day 5, and apheresis was initiated at a CD34+ cell count > 20/μL. Patients with a circulating CD34+ cell count < 20/μL received additional filgrastim on day 6. Cobe spectra apheresis system was used for stem cell collection.

Outcome measures

Mobilization failure was defined as circulating CD34+ cell count < 20/μL up to 6 days after mobilization with G-CSF or patients with a yield < 2.0 × 10^6 CD34+ cells/kg in three apheresis procedures [22]. The average number of CD34+ cells was the arithmetic mean of CD34+ cell counts on all collection days. The number of procedures was the number of collection procedures per patient that were not mobilization failures. The number of collected cells was the total number of collected CD34+ cells per kg body weight of the patient. The dose for a single transplant of 2 × 10^6 CD34+ cells/kg and 3 × 10^6 CD34+ cells/kg was considered the minimum and optimal dose, respectively. For two hematopoietic stem cell transplantations (HSCTs), the double dose of cells was required.

Statistical analysis

The association between the treatment and the defined variables was analyzed using the chi-square test or Student's t-test for independent samples as required. All two-sided p values < 0.05 were considered statistically significant. Statistical analysis was carried out using SPSS v23.

Results

Twenty-eight and 44 patients received induction treatment with VCD and VTD, respectively. Both cohorts were balanced in terms of age, gender, and other disease characteristics (Tab. I). After data on the higher efficacy were available in 2016, VTD was the preferred regimen, which explains the greater number of patients in this group. No difference was observed in the number of induction cycles before mobilization between the two groups. Three patients received local radiation therapy to the spine and one received local radiation to the pelvis. One of the patients in the VTD group, who received radiation to the spine, failed mobilization with G-CSF alone. The mobilization failure rates were 7% and 9% for VCD and VTD, respectively. All patients failing mobilization with G-CSF later

Table I. Patient demographics and baseline characteristics

	VCD	VTD
Total N	28	44
Age, years N (Range)	58 (29-69)	58 (34-70)
Male N (%)	18 (64)	30 (68)
MM stage, ISS N (%)		
1	7 (25)	13 (30)
2	8 (29)	17 (39)
3	12 (43)	10 (23)
Diag. N (%)		
Light Chain only	6 (21)	7 (16)
IgA	10 (36)	8 (18)
IgG	12 (43)	26 (59)
Asecretory	0	3 (7)
Induction cycles N (Median, Range)	3 (3-4)	3 (2-4)
RT before mobilization N (%)	1 (4)	3 (7)
Elev. Creat. at mobilization N (%)	2 (7)	1 (2)
Response after induction		
≥ VGPR	14 (50 %)	28 (64 %)
PR	14 (50 %)	16 (36 %)

MM – multiple myeloma; Diag. – diagnosis; RT – local radiotherapy; VGPR – very good partial response; PR – partial response; Elev. Creat. – elevated creatinine

successfully collected PBSC with chemomobilization or plerixafor. The average number of CD34+ cells in peripheral blood on the day of collection was 60.7 × 10^6/L and 41.1 × 10^6/L, and the number of apheresis procedures was 3 and 2 for VCD and VTD, respectively. The total number of collected stem cells for the VCD and VTD cohort was 7.0 × 10^6/kg and 6.7 × 10^6/kg recipient body weight. In total, 86% of patients receiving VCD induction and 75% of patients receiving VTD induction, collected enough stem cell for at least 2 aHSCTs. The median time to neutrophil engraftment was 13 days in both cohorts. No statistical difference was observed in the number of apheresis procedures, collected cells, the ability to collect a minimum and optimal dose for two aHSCTs, and the time to neutrophil engraftment between the two groups (Tab. II).

Discussion

Triplet induction therapy incorporating novel drugs is standard of treatment for patients with MM [1, 2]. Two commonly used combinations are VTD and VCD [4, 5, 21]. In our center, we use G-CSF only mobilization for patients with MM at first attempt. In patients failing to collect a sufficient number of PBSC, we switch to chemomobilization or the use of plerixafor. There are no published data on the difference between VTD and VCD regarding the effectiveness of G-CSF only mobilization. Owing to unresolved concerns that thalidomide in combination with other agents might impact the efficacy of G-CSF only mobilization, we decided to retrospectively analyze our patient registry and present the data.

The mobilization failure rates for VTD and VCD in our patient group were similar to some reports in the literature [13, 23]. Since G-CSF only mobilization and age > 60 are important predictors for mobilization failure, the low failure rates in our cohort of patients with a median age of 58 years and using G-CSF only mobilization are unexpectedly low [24]. This is likely due to reducing the number of induction cycles to a median of 4 before proceeding to mobilization and not using melphalan as part of the induction regimen, thereby reducing the toxicity to the bone marrow. Approximately 30% of MM patients receive radiation therapy during induction for palliation of bone pain or spinal cord compression [25]. Radiation therapy negatively influences PBSC mobilization and harvest and can even negatively impact overall and PFS [25, 26]. Restraint in radiotherapy in patients eligible for aHSCT treated with novel agents, and novel approaches in radiotherapy have probably decreased the number of mobilization failures in our patient cohort. In our patient cohort, only one patient received radiation therapy prior to successful G-CSF only mobilization (data not shown). All patients failing first mobilization later successfully collected a sufficient number of PBSC with chemomobilization or plerixafor.

The average number of CD34+ cells in peripheral blood on collection day was higher in the VCD cohort than in the VTD cohort; however, the difference was not statistically significant. The lower number of CD34+ stem cells can be attributed to the toxic effects of thalidomide on hematopoietic stem cells [27]. Studies about mice have shown that intermittent dosing of cyclophosphamide has a stem cell sparing effect [28]. Therefore, cyclophosphamide during induction has probably no impact on stem cell mobilization and harvesting. The lack of statistical difference in the number of CD34+ cells in peripheral blood between VTD and VCD can be attributed to the relatively small number of subjects in the study. However, the number of collection procedures and collected stem cell was the same between the cohorts.

Most patients in both groups collected sufficient numbers of PBSC for two aHSCTs. Still, the number of patients achieving an optimal dose for two transplants was only around 60%. Because a higher dose of PBSC is preferred for earlier engraftment with possible lower morbidity, higher numbers of PBSC should be collected [6, 7, 8]. The relatively low number of patients collecting the optimal dose of stem cells for two aHSCTs (6 × 10^6 CD34+ cells/kg) is a weakness of G-CSF only mobilization, and our results are in line with other published results [12, 16, 29]. The addition of plerixafor to G-CSF improves G-CSF mobilization and can increase the number of patients archiving the optimal dose of PBSC for two aHSCTs [29].

To conclude, this study provides further data on VTD safety with respect to stem cell mobilization in comparison with VCD. The addition of thalidomide to bortezomib and dexamethasone showed no negative impact on stem cell mobilization and harvest in patients undergoing G-CSF only mobilization in our patient group.

Table II. Stem cell mobilization and harvest results

	VCD	VTD	
Total	28	44	
Mobilization failure N (%)	2 (7)	4 (9)	$p = 0.771$
Average CD34+ cells in blood on day of collection (Mean x 10^6/L, Range)	60.7 (8.4 - 431)	41.1 (6.45–132.3)	$p = 0.139$
Number of procedures (Median, Range)	3 (0-4)	2 (0-4)	$p = 0.434$
Collected cells (Mean x 10^6/kg, Range)	7.0 (0 – 12.5)	6.7 (0–13.9)	$p = 0.710$
Minimum for two aHSCTs N (%)	24 (86)	33 (75)	$p = 0.275$
Optimal for two aHSCTs N (%)	18 (64)	27 (61)	$p = 0.803$
Time to Neu. engraftment (Median, Range)	13 (10-15)	13 (11–15)	

aHSCT – autologous hematopoietic stem cell transplant; Neu. – neutrophil

Authors' contributions

All authors contributed equally to this work.

Conflict of interest

MSkerget has received speaker honoraria from Amgen, Celgene and Teva Pharmaceutical. BS has received speaker honoraria from Amgen. MSever has received speaker honoraria from Amgen, Celgene and Teva Pharmaceutical.

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Ethics

The work described 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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