A Combination Regimen of Bortezomib, Cyclophosphamide and Betamethasone Gives Quicker, Better and More Durable Response than VAD/CyBet Regimens: Results from a Swedish Retrospective Analysis

Katarina Uttervall^{a, b} Johannes Admasie^{a, b} Evren Alici^{a, b} Johan Lund^{a, b}
Johan Liwing^a Johan Aschan^c Mirjam Barendse^c Stefan Deneberg^{a, b}
Ulf-Henrik Mellqvist^d Kristina Carlson^e Hareth Nahi^{a, b}

^aDivision of Haematology, Department of Medicine, Karolinska Institutet Huddinge, and ^bHaematology Centre Karolinska, Karolinska University Hospital Huddinge, Stockholm, ^cJanssen-Cilag AB, Sollentuna, ^dDepartment of Haematology, Borås Hospital, Borås, and ^eDepartment of Haematology, Uppsala University Hospital, Uppsala, Sweden

Key Words

High-dose therapy · Multiple myeloma · Vincristine, doxorubicin and dexamethasone regimen

Abstract

Background: Induction therapy for multiple myeloma (MM) and remission status before high-dose treatment (HDT) have been shown to be prognostic factors for survival outcome, although the optimal induction therapy is yet to be defined. **Methods:** We conducted a retrospective analysis of the impact of induction therapy on survival outcome before and after HDT in MM patients. The study included 236 consecutive patients who underwent HDT. **Results:** One hundred and forty-two patients (62%) were treated with vincristine, doxorubicin and dexamethasone (VAD) or cyclophosphamide and betamethasone (CyBet) and 94 (38%) were treated with bortezomib, cyclophosphamide and betamethasone (VCB) as induction. Time to first and time to best response was faster in the VCB group than in the VAD/CyBet group, with 42 versus 75 ($p < 0.001$) and 54 versus 88 days ($p < 0.001$), respectively. After induction therapy, 49% of the patients in

the VCB group and 38% in the VAD/CyBet group achieved a very good partial response or better. Multivariate analysis revealed younger age, lower International Staging System stage and induction treatment with VCB as variables associated with favourable time to progression. **Conclusions:** Outcome measured as response and time to progression before and after HDT in MM differs depending on type of induction treatment and suggests that VCB is a highly effective induction regimen that confers a post-HDT advantage.

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Introduction

Multiple myeloma (MM) is a plasma cell malignancy which previously had limited therapeutic options and consequently a poor prognosis. Although the 5-year survival has gradually increased over the last decades, MM is still considered incurable by conventional means. The

K. Uttervall and J. Admasie contributed equally to this work.

goal of therapy for the majority of patients, prolonging survival and preventing progression, is contingent upon achieving the quality of response to therapy and the depth of remissions reached [1, 2].

Allogeneic stem cell transplantation can induce long-term remissions and possibly cure, but because of toxicities and donor availability, there is only limited application for a small subset of patients [3]. In contrast, high-dose therapy (HDT) with melphalan followed by autologous stem cell support is of recognised benefit to younger patients [4, 5] and remains the established standard of care for patients below the age of 65–70 years. To achieve an adequate reduction in disease burden, a so-called induction therapy is given prior to HDT.

The combination of vincristine, doxorubicin and dexamethasone (VAD) [6] has been the standard of care for induction therapy for a long time. Cyclophosphamide combined with dexamethasone was shown to be equally effective but with an improved toxicity profile and with more convenient administration [7]. Therefore, cyclophosphamide combined with dexamethasone, or cyclophosphamide combined with equivalent doses of betamethasone (CyBet), replaced VAD as the standard induction regimen in Sweden and has been used for the past 5 years. The position of CyBet has recently been challenged by the introduction of the so-called novel drugs: thalidomide, bortezomib and lenalidomide.

Bortezomib is a boronic acid dipeptide small-molecule proteasome inhibitor. It promotes apoptosis, prevents DNA repair and inhibits proliferation through actions on several pathways [8]. This clinical activity was described in trials in the early 2000s [9, 10], leading to approval in 2003. Bortezomib has single-agent activity in myeloma [11] and has shown indications of overcoming the resistance to chemotherapy associated with certain cytogenetic abnormalities [12, 13]. With combinations of novel agents and older established drugs, more frequent and deeper responses have been possible. The use of novel-agent combinations has been associated with improvement in survival outcomes following autologous stem cell transplantation (ASCT) [14], fitting with the observation that high-quality responses predict better long-term outcomes [1]. Bortezomib, cyclophosphamide and betamethasone (VCB) were introduced in Sweden during the autumn 2008 and has become widely used in recent years.

The purpose of the present retrospective study was to evaluate the impact of VAD or CyBet compared to VCB as induction treatment for newly diagnosed MM patients eligible for HDT. Data source was unselected consecutive patients from three larger Haematology Institutions in

Sweden. Endpoints studied were response, time to progression (TTP), time to next treatment (TTNT) and overall survival (OS).

Materials and Methods

Study Design and Treatment

The present study was designed as a retrospective comparison of induction treatments. Induction treatment with VCB was compared to VAD and CyBet. VAD and CyBet were combined into a control group since they have been shown to have similar efficacy [7].

VCB was given in 3-week cycles with bortezomib 1.3 mg/m² intravenously on days 1, 4, 8 and 11, cyclophosphamide 1,000 mg/m² intravenously on day 1 and betamethasone 15 mg/day orally on days 1, 2, 4, 5, 8, 9, 11 and 12.

Induction treatment in the control group consisted of either VAD or CyBet. The VAD regimen, vincristine at a dose of 1.6 mg/m² and doxorubicin at a dose of 36 mg/m², was given as a continuous infusion on days 1–4 together with betamethasone at a dose of 30 mg per day on days 1–4, 9–12 and 17–20 and was repeated every 4 weeks [6]. The CyBet regimen was given as cyclophosphamide at a dose of 1,000 mg/m² intravenous infusion for 1 h on day 1 and betamethasone at a dose of 30 mg per day on days 1–4 and 9–12, repeated after 3 weeks. All three regimes are summarised in table 1.

Stem cell mobilization therapy with cyclophosphamide at a dose of 2 g/m² was given after the induction treatment, followed 4 days later by daily subcutaneous injections of filgrastim. The optimal time for harvest was chosen by CD34 monitoring with the objective of collecting $>3 \times 10^6$ CD34-positive cells/kg. The minimum amount requested for a single ASCT was 2×10^6 CD34-positive cells/kg. HDT with melphalan 200 mg/m² was performed within 2–4 weeks after stem cell harvest. After ASCT, no consolidation or maintenance treatment was given.

Study Population

All consecutive patients diagnosed with MM and eligible for HDT between January 2000 and July 2010 at Karolinska University Hospital Huddinge and between January 2005 and July 2010 at Karolinska University Hospital Solna and not included in a clinical MM intervention trial were included. In addition, all VCB induction-treated patients between August 2008 and June 2011 in Borås and Uppsala were included. Patients were excluded from the present study if they were younger than 18 or older than 67 years of age at the time of diagnosis or if the MM treatment or treatment line could not be verified from the medical records. All data were collected from the electronic medical charts of the hospitals or, in the case of death, from the national death register. Patients were followed until death or June 2011. The study has received ethical approval from the local ethical committee in Stockholm.

For each patient, data regarding age, gender, type of myeloma, skeletal destruction, as well as laboratory assessments of calcium, haemoglobin, β_2 -microglobulin, albumin and creatinine were collected at the time of diagnosis (table 2). Patients were censored at the date of allogeneic stem cell transplantation or, in the case of tandem ASCT, at the date of the second HDT. Responses in terms

Table 1. Dosage and administration route of drugs used in the study

	Week 1	Week 2	Week 3	Week 4	Week 5
VCB				next cycle, day 22	
Bortezomib 1.3 mg/m ² i.v.	days 1, 4	days 8, 11			
Cyclophosphamide 1,000 mg/m ² i.v.	day 1				
Betamethasone 15 mg orally	days 1, 2, 4, 5, 8, 9, 11 and 12				
VAD				next cycle, day 29	
Vincristine 1.6 mg/m ² i.v.	days 1–4				
Doxorubicin 36 mg/m ² i.v.	days 1–4				
Dexamethasone 30 mg orally	days 1–4	days 9–12	days 17–20		
CyBet				next cycle, day 22	
Cyclophosphamide 1,000 mg/m ² i.v.	day 1				
Betamethasone 30 mg orally	days 1–4	days 9–12			

i.v. = Intravenously.

of serum M-protein and urine M-protein were collected at baseline and each time the actual measurement differed from the previous measurement. In general, electrophoresis was performed at each patient visit.

Definition of Endpoints and Statistical Methods

Near complete response (nCR) was defined as an immeasurable M-protein by standard electrophoresis (CR was not always confirmed by bone marrow examination as it was not required in the clinical practice), very good partial remission (VGPR) was defined as at least 90% reduction in M-protein, partial response (PR) as at least 50% reduction in M-protein, no response (NR) as less than 50% reduction in M-protein and progressive disease (PD) as 25% increase in M-protein, according to International Myeloma Working Group criteria [15]. TTP was defined as the time between the start of first-line treatment until PD. TTNT was defined as the time between the start of the first treatment and the start of the next treatment. OS, TTP and TTNT were calculated with the Kaplan-Meier method and compared using the log-rank test. The variables predicting TTP, TTNT and OS were evaluated using Cox regression models to estimate hazard ratios. First, univariate risk factors were analysed and the significant risk factors at the $p < 0.05$ level were included in the subsequent multivariate model. All p values were two-tailed. Analysis was performed using Statistica software (StatSoft, Tulsa, Okla., USA).

The primary endpoint was TTP. Response rates (nCR, VGPR, PR, NR and PD) before and after HDT, time to first and best response, TTNT and OS were secondary endpoints. Time to first and best response, TTP, TTNT and OS were calculated from the start of first-line treatment to the date of a PR or better (time to first response), to the best response obtained, to the date of PD or the start of second-line treatment (TTP), start of second-line treatment (TTNT), or death or last follow-up (OS).

Fluorescent in situ Hybridization

Fluorescent in situ hybridization (FISH) was performed on unstimulated bone marrow cells cultured for 12 h with cell mag-

Table 2. Patient characteristics

	VCB (n = 88)		Control group (n = 146)		p
	n	%	n	%	
Age, years					<0.01
Median	50		56		
Range	32–67		36–67		
Males	55	62	81	63	0.9
Type of MM protein					
IgG	48	55	73	57	0.7
BJ	18	20	25	19	0.8
IgA	16	18	23	18	0.9
Other	6	7	8	6	0.8
ISS					
I/II	69	84	102	87	0.03
III	13	16	15	13	
Serum creatinine					
<1.8 mg/dl	77	88	117	91	0.7
>1.8 mg/dl	11	12	12	9	
Haemoglobin					
>10 g/dl	24	27	37	29	0.6
<10 g/dl	64	73	92	71	
Bone lesion		83		68	0.02

netic separation by CD138. A minimum of 200 interphase nuclei were assessed during each hybridization procedure. Normal donor cells (peripheral blood mononuclear cells) were used as control. Del.13 was defined as the presence of more than 20% mono-allelic cells for the specific probe among the plasma cells. FISH analysis was performed using the following probes: 13q14.3 deletion probe (13qter clone 163c9) from Cytocell.

Table 3. Time to first response and time to best response

	Median VCB (n = 88)	Median VAD/CyBet (n = 129)	P
Time to first response before HDT, days	32 (8–133)	57 (9–195)	<0.001
Time to best response before HDT, days	43 (8–133)	65 (9–195)	<0.001

Figures in parentheses are ranges.

Table 4. Type of response to induction and HDT treatment

Type of response	VCB before HDT		VAD/CyBet before HDT	
	n	%	n	%
nCR	20	23	18	14
VGPR	23	26	31	24
PR	40	45	74	57
NR	5	6	6	5
Total	88	100	129	100
Type of response	VCB after HDT		VAD/CyBet after HDT	
	n	%	n	%
nCR	51	58	57	44
VGPR	31	35	40	31
PR	4	5	30	23
NR	2	2	2	2
Total	88	100	129	100
Type of response	VCB before/after HDT, %		VAD/CyBet before/after HDT, %	
≥VGPR	49/93		38/75	
≤VGPR	51/7		62/25	
Total	100/100		100/100	

Results

Patients

Our study population consisted of 236 patients, 94 of whom were treated with VCB and 142 were in the control group. In total, 6 of the patients (6%) from the VCB-treated group and 13 (9%) of the patients in the control group

had their induction treatment changed because of intolerance or NR. These were included in the OS analysis but excluded from further analysis. This resulted in a final population of 217 patients, including 88 treated with VCB and 129 in the control group. Two patients in the VAD/CyBet group were lost to follow-up and were censored on the date they were last confirmed to be alive.

VCB was given with a median of 3 courses (range 1–5) and, in the control group, VAD or CyBet was given with a median of 4 courses (range 2–6). There was no difference in median TTP (2.6 vs. 2.1 years) or OS (6.9 years vs. not reached; no difference, but shorter observation time for the CyBet group) between patients treated with VAD compared to those treated with CyBet in the control group. Furthermore, there were no statistically significant differences in TTP or OS between the patients in the VCB group depending on the centre in which they were treated (data not shown).

The patients in the VCB group were younger, with a median of 50 compared to 56 years, but with a more advanced International Staging System (ISS) stage. Furthermore, bone lesions were more common among VCB-treated patients. However, at the time of VAD/CyBet, a simple X-ray was taken, while nowadays, the more sensitive CT scan is the preferred method to evaluate bone lesions.

Response before and after HDT

Time to first response was significantly shorter for the VCB-treated patients at 32 days, compared with 57 days for the control group ($p < 0.001$). The time to best response was 43 and 65 days, respectively ($p < 0.001$; table 3).

In the VCB-treated patients, the response rate before HDT, measured as nCR/VGPR/PR/NR%, was 23/26/45/6 compared with 58/35/5/2 after HDT. In the control group, the corresponding response rate was 14/24/57/5 before and 44/31/23/2 after HDT. The VCB population showed significantly better ≥VGPR versus the control group, both before and after HDT (49/93 and 38/75, respectively; table 4). The responses after HDT improved in both groups, although the improvement was slightly better in the VCB compared to the control group (45 vs. 32%).

TTP, TTNT and OS

At study cut-off in June 2011, 84 patients (96%) in the VCB group were alive compared to 95 (74%) in the control group (not significant). The median follow-up time of surviving patients was 42 and 40 months for all patients.

Fig. 1. Effect of VCB versus VAD or CyBet induction treatment on TTP (a), OS (b) and TTNT (c) of patients with MM receiving ASCT. There was a statistically significant difference in TTP between the groups, but not in OS and TTNT.

In the VCB group, the median follow-up time of the surviving patients was 20 and 19 months for all VCB-treated patients.

The median TTP/TTNT was not reached in the VCB-treated patients but was 2.46/2.9 years in the control group (fig. 1, 2). There was a significantly improved TTP in the VCB group compared to the control group ($p < 0.017$). There was also a difference in TTNT in favour of VCB, although this was not statistically significant ($p < 0.111$).

Median OS was not reached for the VCB-treated patients, compared to 6.65 years for the control group (not significant; fig. 1b). The number of patients discontinuing induction treatment because of treatment toxicity or disease progression during initial therapy was slightly lower in the VCB group compared with the control group (6 vs. 9%), but was not significantly different.

Cox Regression Analysis

VCB as induction therapy was the only factor affecting response before HDT in univariate analysis ($p < 0.002$ for first response and $p < 0.005$ for best response before HDT).

The difference in TTP was the only outcome among TTP, TTNT and OS that was significantly different between VCB and the control group. Therefore, univariate and multivariate risk factor analyses were only carried out for TTP. Univariate analysis showed that age, ISS and bone lesions were significantly affecting TTP. Multivariate analysis showed that type of treatment was the most significant factor for TTP ($p < 0.0001$); age and ISS were also significant ($p < 0.002$ and < 0.0002 , respectively), but not bone lesion ($p < 0.13$; table 5).

Fig. 2. Effect of del.13 on TTP (a), OS (b) and TTNT (c) in patients receiving VAD/CyBet as induction prior to ASCT. Patients without any information on del.13 were also plotted (gray streaked line). There was a statistically significant difference in TTP and OS between the groups, but no difference in TTNT.

Table 5. Multivariate analysis, dependent variable: TTP (n = 217)

	β	p	Risk ratio	Risk ratio 95% lower limit	Risk ratio 95% upper limit
Bone lesions, no/yes	-0.39	0.13	0.68	0.411	1.117
Age, as a continuous variable	-0.04	0.002	0.98	0.931	0.983
ISS: I, II, III	0.61	0.0002	1.84	1.331	2.562
Treatment VCB/VAD, CyBet	1.46	<0.0001	4.3	2.136	8.738

Del.13 Analysis

In the VAD/CyBet era, FISH analysis was only performed on del.13q14. Bone marrow samples from 57 patients were analysed for del.13. According to FISH results, 18 patients had del.13 and 39 patients were negative. Thus, using the probe described above with a 20%

cut-off level, 32% of the patients carried del.13 at the time of diagnosis.

Median TTP, OS and TTNT in the del.13 group treated with VAD/CyBet were 1.9, 4.3 and 2.2 years and, in the non-del.13 group, 3.1, not reached and 3.1 years, respectively (fig. 2). In order to demonstrate that there was no

Fig. 3. The effect of del.13 on TTP in patients receiving VCB and VAD/CyBet as induction prior to ASCT. It seems that OS improves for both patients with and without del.13 by using VCB induction.

selection bias between the patients who were cytogenetically analysed for del.13 and those who were not, the TTP, OS and TTNT curves for the non-evaluated group are also plotted in the same figures.

In the VCB group, FISH analysis was performed on del.13q14 in 34 patients and del.13 was found in 13 patients (38%). At median follow-up time, there was no difference in TTP, OS or TTNT in any of the above-mentioned groups.

The 2-year TTP in the VCB and VAD/CyBet group for patients with del.13 was 82 and 43%, while patients without del.13 had a 2-year TTP of 95 and 77%, respectively (fig. 3).

Discussion

We designed this retrospective study to investigate whether, in a real-life patient setting, the combination of bortezomib with corticosteroids and an alkylating agent (cyclophosphamide) would result in an improved response rate as well as in deeper responses both before and after HDT. We chose to compare it with conventional VAD/CyBet, as these were the standard induction regimens used in Sweden. We could demonstrate that there was a significant difference in the number of patients reaching $\geq$ VGPR both before and after HDT: 49 and 93%

for patients treated with VCB compared with 38 and 75% for patients in the control group, respectively.

One drawback of the present study is that it used data from VCB-treated patients from three different centres while the control group consisted of patients from only one centre. This was done to increase the number of patients in the VCB group and, since the treatment outcomes in the VCB groups did not differ between the participating centres, the selection bias effect is probably small. Furthermore, the control group consisted of patients treated with two different regimens. However, it was previously shown that those treatments are similar, and we were able to verify that finding in the current study. Therefore, we estimate this effect to be small as well. Since all consecutive patients were included from three centres in Sweden, we believe it is a representative cohort of HDT-treated patients in Sweden. The VCB population was younger and had a higher ISS score, but the type of induction treatment had a greater impact on TTP in multivariate analysis.

A strength of the current trial is the real-life setting. We analysed all consecutive patients with newly diagnosed MM receiving induction treatment with the intent to proceed to HDT. Therefore, the study population represents the clinical reality and complements the data from prospective randomised trials that usually consist of highly selected patients.

Two-drug combinations including a novel agent and a corticosteroid have been established as induction therapy in MM before HDT. Bortezomib plus dexamethasone significantly improved post-induction and post-transplantation CR/nCR and at least VGPR rates compared with VAD and resulted in a trend for longer progression-free survival [16]. Thalidomide and dexamethasone, although viable and more effective than classical chemotherapy or steroids alone, has lower response numbers and is inferior to at least one bortezomib-containing regimen [17, 18]. Several three-drug combinations, including one novel agent, have shown high efficacy. VCD has recently shown high proportions of response in a large uncontrolled trial [19]: as cyclophosphamide plus bortezomib plus dexamethasone (CyBorD) in a smaller study [20], as two separate regimens (VCD and VCD-mod) in a four-arm randomised trial [21], and with bortezomib in weekly administration in an uncontrolled trial [22]. Thalidomide and dexamethasone combined with doxorubicin has shown superiority over VAD [23], and bortezomib, thalidomide and dexamethasone have shown excellent activity and superiority over both thalidomide and dexamethasone [17] and classic chemotherapy [24]. Bortezomib together with doxorubicin and dexamethasone has been tried in a randomised con-

trolled trial, showing superiority to the old standard VAD [25] and was also tried in three single-arm trials [26].

As for toxicity, the number of patients discontinuing induction treatment because of treatment toxicity or disease progression during initial therapy was slightly lower in the VCB group compared to the control group, but the numbers were small and should be interpreted with care. However, this is important since the optimal induction therapy should give good disease control with limited toxicity in order to allow patients to proceed to the HDT. Significant differences in efficacy, measured as response, TTP, but not OS, were observed between the treatment groups. The lack of difference in OS could be due to insufficient observation time within the VCB group. Therefore, longer follow-up is needed. The feasibility of the VCB regimen, with a low degree of toxicity and fast and deep responses, has made it an attractive alternative among patients and doctors in Sweden. A prospective randomised trial comparing VCB to other three-drug regimens is warranted.

Regarding response before and after HDT, a very important question is: does response before HDT matter? A recent French study found response prior to HDT to be correlated with improved relapse-free survival after HDT [27]. Our own data support this finding, with VCB patients having better responses measured as $\geq$ VGPR both before and after HDT and improved TTP, and this was also shown in a recent International Myeloma Foundation trial [28].

In the multivariate analysis of response before HDT, VCB as induction therapy was the only factor of impor-

tance. We were able to show a clear improvement in TTP in VCB-treated patients compared to VAD/CyBet, and in the multivariate analysis of factors influencing TTP, VCB was shown to have a significant impact together with age and ISS score.

We found a prevalence of 38% del.13q14 in the present study. No difference was found in TTP, OS or TTNT in the VCB group in our material, but the number of patients examined was small with a short median follow-up time. Detection of monosomy and deletions of 13q has for many years been considered to be an adverse prognostic factor in MM patients. Fifteen years ago, Tricot and colleagues [29] described the negative impact of deletion of the long arm or the whole chromosome 13 on survival in MM patients. However, the loss of 13q is not an independent prognostic factor in almost all new studies using FISH when different cytogenetic aberrations are to be considered in a multivariate analysis. In our study, this marker was analysed in 39% of the patients in the control group. Del.13 had a significant negative impact on both TTP and OS in patients treated with VAD/CyBet.

In conclusion, the current study identified differences in terms of improved response and TTP between VCB and VAD/CyBet as initial treatment for patients with newly diagnosed MM. The proportion of patients undergoing HDT was higher with VCB and toxicity was limited. VCB was found to be a highly effective induction regimen that confers a post-HDT advantage. In Sweden, 2–4 cycles of VCB is currently considered the standard induction therapy.

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