

New salvage vincristine, carmustine, cyclophosphamide, and prednisone (VBCP) chemotherapy for relapsed/refractory multiple myeloma in the modern era: A case series

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Abstract

We report our experience with vincristine, carmustine (BCNU), cyclophosphamide, and prednisone (VBCP), a regimen given in the outpatient setting to patients with multiple myeloma (MM) resistant to almost all the available novel/targeted therapies. Ten patients received salvage VBCP who were heavily pretreated with a median of 5.5 prior treatment regimens including lenalidomide, pomalidomide, bortezomib, carfilzomib, cyclophosphamide, and autologous stem cell transplantation. The objective response rate (\geq PR) was 60%, with an additional 30% achieving stable disease (SD). The median time to progression for patients with \geq SD was 3.6 months. The median progression free survival was 4.4 months while the median overall survival was 12.8 months. Despite severe myelosuppression being the main toxicity, 61% of the subsequent cycles were given on time. Treatment-related mortality was not observed. Our results suggest VBCP is a highly active and tolerable salvage regimen among heavily pretreated MM patients who already failed many of the novel agents.

Keywords: multiple myeloma; novel agents; salvage therapy; BCNU; autologous stem cell transplantation

Introduction

Over 30,000 new cases of multiple myeloma (MM) were diagnosed in 2016 in the USA, and it remained the second most common hematologic malignancy diagnosed after chronic lymphocytic leukemia [1]. Since 2015, four new drugs were approved for the treatment of relapsed/refractory MM: panobinostat, daratumumab, ixazomib, and elotuzumab. Additionally, there were regulatory approvals for carfilzomib-based and daratumumab-based combination therapy in relapsed/refractory myeloma as well as for lenalidomide maintenance therapy after autologous transplantation. In the carfilzomib-based and daratumumab-based regulatory trials, combination therapy resulted in unprecedented complete response (CR) rates ranging 20-40% [2-4]. However, relapse remains common and highlights the need for additional treatment options when patients progress on novel anti-myeloma therapy. These options include enrollment in a clinical trial, re-challenging with previously used agents, salvage autologous stem cell transplantation (ASCT), or salvage chemotherapy.

Several salvage high-intensity chemotherapy options have been designed to rapidly control progressive myeloma. Among the listed options in the National Comprehensive Cancer Network multiple myeloma guidelines are dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP), bortezomib, thalidomide, dexamethasone,

cisplatin, doxorubicin, cyclophosphamide, and etoposide (VTD-PACE) or another variation such as DT-PACE without bortezomib. Another older treatment option that can be considered is vincristine, carmustine (BCNU), melphalan, cyclophosphamide, and prednisone (VBMCP) [5].

VBMCP was devised as a means of improving response rates over melphalan and prednisone (MP) [6]. Melphalan has been used to treat patients with MM for over half a century [7]. Two large meta-analysis were conducted in the 1990s to determine if there was any benefit of melphalan-based combination chemotherapy (CCT) compared to MP in patients with newly diagnosed myeloma. In the publication by Gregory et al., there was no significant

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difference in overall survival between melphalan-based CCT and MP, however MP was inferior for those patients with a poor prognosis [8]. On the other hand, there was no evidence that poor-risk patients benefited more from CCT when the Myeloma Trialists' Collaborative Group conducted their meta-analysis [9]. None-the-less, large trials like the Eastern Cooperative Oncology Group (ECOG) E2479 study found VBMCP more effective than MP in producing and sustaining remission in patients with MM [5]. However, melphalan has significant hematologic dose-limiting toxicity; the leukopenia and thrombocytopenia observed with melphalan can be delayed and prolonged, which is the reason behind giving the regimen every 35 days. Thus, we wanted to modify this regimen and avoid melphalan due its prolonged myelosuppression and its known leukemogenic and potentially mutagenic effects.

The VBMCP regimen consists of vincristine 1.2 mg/m² IV day 1, carmustine (BCNU) 20 mg/m² IV day 1, melphalan 8 mg/m² PO days 1-4, cyclophosphamide 400 mg/m² IV day 1, and prednisone 40 mg/m² PO days 1-7, given every 35 days. In our new regimen, VBCP, melphalan is omitted and cyclophosphamide 400 mg/m² IV is given days 1-4 in 28-35 day cycle. We report our limited experience with this salvage regimen in heavily pretreated MM patients who failed almost all the available novel and targeted therapies.

Patients and methods

Patient selection

We conducted a retrospective, IRB approved study (IRB201601388), in which case records of patients with relapsed/refractory MM treated with BCNU containing regimens at the University of Florida from January 1, 2006 onwards were reviewed. Patients were identified using institutional databases and were included if they received at least one cycle of above therapy. Pre specified clinical information was obtained from the same databases, including age, sex, date of birth, race, Karnofsky performance status (KPS), laboratory and radiologic data, bone marrow biopsy, cytogenetics/fluorescence in situ hybridization results, prior lines of therapy, time to progression, progression free survival (PFS), and overall survival (OS).

Treatment and response evaluation

Only patients who received the combination VBCP, a modification of VBMCP, were included in the analysis, while all other carmustine containing regimens such as VBMCP were excluded. Patients were treated in the outpatient infusion center. VBCP regimen includes vincristine 1.2 mg/m² (not to exceed 2.0 mg) IV day 1, BCNU 20 mg/m² IV day 1, cyclophosphamide 400 mg/m² IV days 1-4, and prednisone 40 mg/m² days 1-7, given every 28-35 days. Growth factor support was given to all patients either with daily filgrastim or pegfilgrastim. Response was graded using the International Myeloma Working Group (IMWG) uniform response criteria [10]. Toxicity was assessed using the Cancer Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Statistics

Descriptive statistics (median, range, and proportions)

were used to describe the patient characteristics, response rates, and frequency of toxicities. PFS was assessed from the start of VBCP chemotherapy to the date of progression or date of death. OS was calculated to the date of death due to any cause. Patients alive without progression or living were censored on the date of last follow-up for PFS or OS, respectively. Median PFS and OS were estimated by Kaplan-Meier method. Statistical analysis was performed using SPSS Statistics software version 24 (IBM Corp, released 2016).

Results

Patient characteristics

Ten patients with a diagnosis of MM who received VBCP chemotherapy between January 1, 2006 and August 31, 2016 were identified. All patients were treated in the outpatient setting and hospitalized once developed neutropenic fever or other significant complications. Patient characteristics are listed in Table 1. The median age at

Table 1 Baseline characteristics of patients receiving VBCP chemotherapy (n = 10).

<i>Characteristic</i>	
Age at diagnosis, median (range)	63 (51-73)
Male, n (%)	5 (50)
Female, n (%)	5 (50)
Race, n (%)	
Caucasian	5 (50)
African American	5 (50)
ISS stage at diagnosis, n (%)	
I	4 (40)
II	4 (40)
III	2 (20)
High-risk features at diagnosis, n (%)	
Extramedullary disease	1 (10)
Extramedullary disease at time of VBCP	2 (20)
High risk cytogenetics* at diagnosis	2 (20)
M-spike type, n (%)	
IgG	7 (70)
IgA	1 (10)
Kappa only	2 (20)
Karnofsky score, median (range)	70 (60-80)
Prior therapies, n	
Thalidomide	3
Lenalidomide	10
Pomalidomide	6
Bortezomib	10
Carfilzomib	8
Cyclophosphamide	9
Autologous stem cell transplant, single	9
Autologous stem cell transplant, salvage	3
Number of prior regimens, median (range)	5.5 (4-11)

*High-risk cytogenetics: del (17p), t (4;14), t (14;16) on FISH

diagnosis of multiple myeloma was 63 with five males and five females, and an equal distribution of Caucasian and African Americans. According to the International Staging System (ISS), four patients had stage 1, four patients had stage 2, and two had stage 3 disease at the time of initial diagnosis. Most had a good KPS at enrollment (median of 70%). Patients were heavily pretreated with a median of 5.5 prior regimen (range, 4 – 11). Greater than 90% of patients were previously exposed to lenalidomide, bortezomib, and an alkylating agent. Six (60%) patients were previously treated with pomalidomide and 8 (80%) patients were previously treated with carfilzomib. Nine patients (90%) had undergone one autologous stem cell transplant (ASCT)

after diagnosis and three (30%) had salvage 2nd ASCT, all prior to VBCP chemotherapy.

Treatment characteristics and disease response

The objective response rate (ORR, ≥ partial response) was 60% with an additional 30% achieving minimal response or stable disease (Table 2). One patient had progressive disease. The median time to response for patients with at least a partial response was 1.2 months (range, 0.4 – 2.4 months) and the median time to progression (TTP) for patients with stable disease or better was 3.6 months (range, 0.7- > 38.9 months). The median PFS was 4.4 months (95% CI 1.32 – 7.48) and the median OS was 12.8 months (95% CI 4.03 – 21.63) (Figure 1).

Table 2 Patients response to VBCP chemotherapy.

Patient	Time from Dx to VBCP (months)	Number of prior lines of therapy	Best response	Number of cycles	TTP (months)	Next line of therapy	A/D
A	51.6	4	VGPR	3	8.2	Salvage ASCT	D
B	22.5	5	PD	3	1.2	VTD-PCE	D
C	19.7	4	MR	1	0.8	Salvage ASCT	A
D	70.9	9	PR	5	2.9	Hospice (progressive neuropathy)	D
E	117.1	9	VGPR	Ongoing (> 15)	Not reached (> 39)	Ongoing	A
F	72.4	6	VGPR	8	6.7	Daratumumab	D
G	45.7	5	PR	3	3.6	Salvage ASCT	A
H	75.7	11	SD	1	0.7	Melphalan + Dex	A
I	176.5	6	SD	4	8.8	Pomalidomide + Bortezomib + Dex	D
J	23.8	5	PR*	1	Not reached	Daratumumab	A

Abbreviations: A/D – alive/dead; ASCT – autologous stem cell transplantation; Dex – dexamethasone; Dx – diagnosis; MR – minimal response; PR – partial response; SD – stable disease; TTP – time to progression; Tx – Therapy; VGPR – very good partial response; VTD-PCE – bortezomib, thalidomide, dexamethasone, cisplatin, cyclophosphamide, etoposide.

*Patient had near complete resolution of innumerable subcutaneous plasmacytomas, largest was about 10 cm Rt submandibular mass.

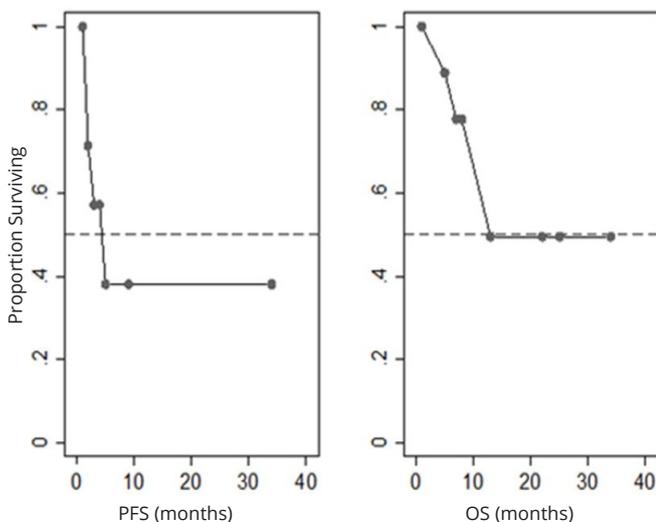


Figure 1 Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) for patients treated with VBCP chemotherapy.

Toxicities to VBCP chemotherapy

This combination was in general well tolerated and 61% of the treatment cycles were given on time, every 28-35 days.

Delay in blood count recovery and hospitalization due to neutropenic fever were the main reasons for delaying the next cycle beyond 35 days from prior cycle. Treatment-related adverse events are presented in Table 3. Grade 3 and 4 hematologic toxicities were common with transfusion-requiring anemia encountered in 50% of patients and neutropenia and thrombocytopenia encountered in 60% of patients. Neutropenic fever was observed in 20% of patients. Grade 3-4 infection without neutropenia occurred in 50% of patients. Hematologic myelosuppression was the reason for reducing the cyclophosphamide dose to two days (50%) in 20% of patients. Other non-hematologic complications of VBCP chemotherapy included electrolyte abnormalities, renal insufficiency, tumor lysis, neuropathy, vomiting, and atrial fibrillation. No treatment-related mortality (TRM) was observed.

Discussion

Vast progress has been made in the treatment of patients with MM, perhaps more than any other malignancy. The number of approved agents has rapidly grown so that treating oncologists face new challenges in the management of relapsed/refractory disease. Among those

Table 3 VBCP chemotherapy toxicity (n = 10).

Toxicity	Grades 1-2, %	Grade 3, %	Grade 4, %
Anemia	20	50	
Thrombocytopenia		50	10
Neutropenia	10	30	30
Neutropenic fever		20	
Upper resp infection	10		
Lung infection		10	
Skin infection		10	
Enterocolitis		20	
Infection, other	20	10	
Vomiting	30		
Atrial fibrillation		10	
Hyponatremia	10	10	
Hypokalemia	20		
Hypophosphatemia		20	10
Hypomagnesemia	10		
Acute kidney Injury	10		
Tumor lysis		10	
Neuropathy		20	

challenges is the optimal therapy of multiply relapsed/refractory myeloma (RRMM). Prior to the development of newer generation immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies, relapsed disease was often treated with combination chemotherapy. In this study, we present results of retrospective analysis on heavily pretreated patients with RRMM who received a new VBCP salvage chemotherapy, which is modified from VBMCP regimen.

In this study, patients treated with VBCP had an ORR of 60% and an additional 30% achieved minimal response or stable disease. These were more heavily pretreated with a median of 5.5 prior regimens. Almost all of the patients were previously treated with lenalidomide, bortezomib, carfilzomib, pomalidomide, and cyclophosphamide as well as 1-2 ASCTs. The PFS observed in these patients was 4.4 months and the median OS was 12.8 months. The short time to best response, the high ORR, but short PFS suggests that the main utility of salvage VBCP is to achieve quick control of the disease and as a bridge to novel myeloma therapy including salvage ASCT and the new approved drugs such as the monoclonal antibodies. Indeed, for 30% of the patients, VBCP was used as a bridge to salvage ASCT. One patient was subsequently treated with daratumumab after relapsing on therapy while another patient was able to be switched to daratumumab therapy as a more convenient treatment/maintenance in the outpatient. One patient was subsequently treated with pomalidomide-based therapy while two others required other salvage chemotherapy. Of interest, one patient previously treated with 9 lines of therapy has been maintained on VBCP therapy for over three years and has remained in continuous very good partial response (VGPR). In this patient, in order to minimize toxicity while continuing this effective therapy, VBCP was dose-adjusted and the frequency of administration was extended to every 8 weeks with sustained response.

VBCP effectiveness seems equivalent to other salvage chemotherapy combinations, such as VTD-PACE and

hyperCVAD, used in our practice, but with the advantage of being able to give VBCP in the outpatient setting as opposed to the other two regimens that have to be given in the inpatient setting. All these regimens are used interchangeably in our practice, however we have seen patients who failed VTD-PACE or hyperCVAD responding to VBCP. Furthermore, VBCP effectiveness also seems equivalent or better in comparison to other published salvage chemotherapy regimens and in similar MM patient population. Most patients diagnosed with myeloma in the modern era are not exposed to classic chemotherapy agents which usually has different mechanism of action than that of novel agents. Thus, the use of this drug combination later in the salvage setting may improve the survival of these patients. A number of groups have highlighted their experience with different combination salvage therapies in patients with aggressive or RRMM in the modern era. Gerrie et al. reported data on the use of dexamethasone ± thalidomide with infusion of cisplatin, doxorubicin, cyclophosphamide, and etoposide [D(T) PACE] in patients with a median of three prior treatment regimens [11]. In their review of data from 75 patients, the ORR was 49% while another 36% had either minimal response or stable disease. The PFS was 5.5 months and the OS was 14 months. Subsequently, another report on 51 patients highlighted the utility of dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) in this type of patients [12]. The ORR was 45% with the majority of patients achieving better than partial response while 33% had minimal response or stable disease. As with the prior study, patients had a median of 3 prior treatment regimens. The median PFS was 3.7 months and the median OS was 8.0 months. Finally, in a comparative study, outcomes with DCEP, VTD-PACE, and cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD) salvage were reported [13]. The ORR were 52%, 73%, and 49%, respectively. These patients were treated with a median of 3 prior regimens.

Toxicity was fairly common with VBCP chemotherapy. As expected in this heavily pretreated MM patients, grade 3-4 myelosuppression was the most common toxicity. This is most likely caused by the quadrupling the cyclophosphamide dose from one day to 4 days. Twenty percent of patients had neutropenic fever while another 50% had non-neutropenic infections mainly of skin, respiratory or gastrointestinal tract. Serious non-infectious toxicity included electrolyte abnormalities, renal injury, tumor lysis, and atrial fibrillation. One patient had debilitating neuropathy and transitioned to hospice care after VBCP chemotherapy. Pulmonary toxicity was not observed.

The VBCP regimen consists of vincristine, BCNU, cyclophosphamide, and prednisone. Compared to VBMCP, the dose of cyclophosphamide is increased and melphalan is omitted. While direct comparison is not possible, VBMCP chemotherapy toxicity included leukopenia in 22 of 46 patients and combined leukopenia and thrombocytopenia in an additional 10 patients requiring dose reductions and treatment delay in patients with melphalan-resistant myeloma [14]. VBMCP induction and consolidation therapy in patients with newly diagnosed MM resulted in grade 3 or

higher hematologic toxicity in 72% of patients in the study by Kyle et al. [15]. Our decision to omit melphalan from the regimen was based on the fear that the prolonged nadir of melphalan-induced myelosuppression will delay treatment and cause more prolonged long-term marrow toxicity. In our heavily pretreated patients managed with VBCP chemotherapy, 80% of patients had grade ≥ 3 hematologic toxicity. Despite that, 61% of the subsequent cycles were given on time.

BCNU is one of the agents that differentiate VBCP from DCEP, VTD-PACE, and CVAD. Like cyclophosphamide, melphalan, and cisplatin, BCNU is an alkylating agent that has been used in the treatment of MM in different combinations. These published combinations include BCNU, doxorubicin, and prednisone (BAP) [16], vincristine, BCNU, doxorubicin, and prednisone or dexamethasone (VBAP/VBAD) [17–19]. In phase I/II study, BCNU (300 mg/m²) was used with high-dose melphalan conditioning regimen prior to ASCT [20]. By adding etoposide and BCNU to melphalan conditioning, a CR rate post BEM-autologous stem cell transplantation was 64% with an ORR of 97% [21]. Finally, V-BEAM (bortezomib-BEAM) conditioning prior to second ASCT for RRMM produced a CR rate at day +100 of 75% [22]. However, due to unexpected treatment-related toxicity of infectious colitis, neutropenic colitis, and overwhelming sepsis, the study was terminated after enrolling 10 patients.

Conclusions

Although our study is limited by the small size of patients and retrospective nature, our analysis suggests VBCP is efficacious in producing an objective response with tolerable side effects in heavily pretreated population of RRMM. VBCP can be considered as a salvage option for patients who do not qualify for clinical trials, are awaiting clearance for novel anti-myeloma therapy, or have rapidly progressive disease.

Conflicts of interest

We have no conflicts of interest to disclose.

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