

Use of carfilzomib in second-line therapy and beyond for relapsed multiple myeloma

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Abstract: The development of proteasome inhibitors has been a major advance in therapy of multiple myeloma, accounting, in part, for the significant increase in the survival of patients diagnosed with this disease. Bortezomib was the first proteasome inhibitor to be approved for the therapy of multiple myeloma. Carfilzomib is a second-generation proteasome inhibitor with irreversible binding to proteasome and less off-target toxicity. The drug has been approved for use in relapsed/refractory multiple myeloma. In this article, we review the use of carfilzomib as second-line therapy in multiple myeloma. We also review the current standards of care for relapsed/refractory multiple myeloma, with particular focus on the use of carfilzomib in advanced disease.

Keywords: multiple myeloma, carfilzomib, relapsed/refractory

Introduction to the management of relapsed and refractory multiple myeloma

Over the past two decades, improvements in therapy have led to improved outcomes for people with multiple myeloma. According to the SEER database, the percentage of newly diagnosed patients surviving beyond 5 years from diagnosis increased from 30% in 1999 to 48.5% in 2012.¹ The major reason for this development has been discovery and widespread implementation of novel agents, namely proteasome inhibitors and immunomodulatory drugs, during that period. Novel therapeutic combinations incorporating these newer drugs have yielded impressive results, with overall response rates approaching in excess of 80%–90% and rates of complete remission (CR) approaching as high as 40%–50%.^{2–5} Despite these improvements in frontline therapy, multiple myeloma remains incurable and relapse after frontline therapy remains the norm in the majority of the patients.

The treatment of relapsed and refractory myeloma, thus, remains a very large and important part of management of patients with this disease.⁶ Most patients require multiple lines of therapy during their disease course. In this review, after briefly outlining the current and emerging therapeutic options for patients with relapsed and/or refractory multiple myeloma, we will specifically focus on the use of carfilzomib as second-line therapy.

Overview of current treatment approaches Drug combinations available for use in relapsed or refractory multiple myeloma

Multiple drugs are approved for use in this patient population either as single agents or in combination, including melphalan, cyclophosphamide, thalidomide, lenalidomide, pomalidomide, bortezomib, carfilzomib, ixazomib, liposomal doxorubicin, panobi-

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nostat, elotuzumab, and daratumumab. Pivotal randomized trials establishing the use of many of these agents are detailed in Table 1. Table 2 provides a list of noteworthy Phase 1 and Phase 2 trials that incorporate one or more of these agents. One important observation from these trials is that with newer drug combinations, the response rates are quite high even in relapsed/refractory setting. Although differences in inclusion/exclusion criteria and the resultant variability in the patient populations make it impossible to directly compare the results of specific trials, it is evident that several regimens induce responses in $\geq 70\%$ of treated patients. Furthermore, the quality of responses (as assessed by the frequency of achieving at least a very good partial response [VGPR]) is improving. As an example, the likelihood of achieving at least a VGPR with recent triplet regimens^{7,8–10} is 2–3 times higher than with single-agent bortezomib,^{11–13} and 10 times higher than with dexamethasone alone.^{14,15} Finally, disease control may be prolonged, particularly as some of the noted regimens incorporate ongoing maintenance therapy.^{9,10,16}

Two-drug vs three-drug regimens

As various combination regimens have been developed for the treatment of patients with relapsed/refractory multiple

myeloma, optimal use of the specific drugs has become a subject of controversy. A perusal of Tables 1 and 2 shows that both two-drug (doublet) and three-drug (triplet) regimens are superior to single-agent therapy in this setting. Furthermore, most of the included trials comparing triplets to doublets demonstrate overall superiority of three-drug combinations in terms of initial response rate and duration of response. But the question of survival benefit remains a difficult one given that all these drugs would be available to the patients at the time of progression and the clinical trials are not designed to compare sequential treatments. In addition, the data for overall survival (OS) are not completely mature in many of the randomized trials comparing three- vs two-drug combinations.^{7,8–10,17,18} Thus, it is unclear at this time whether three-drug regimens would lead to superior survival as long as patients eventually have access to all available therapies. Another relevant consideration is the potential for increased toxicity as additional drugs are added to a regimen. Tables like the ones herein rarely provide insight with regards to this aspect of therapy selection, instead focusing on efficacy end points. Particularly in older and/or frail patients, the toxicity profile of specific combinations should be carefully considered and balanced against the incremental improvement in expected immediate disease control.

Table 1 Regimens for relapsed refractory multiple myeloma therapy based on Phase 3 randomized trial data

Trial	ORR/VGPR+ (%)	PFS (months)	OS (months) ^a	References
Bor vs Dex	38/7 18/1	6.2 3.5	29.8 23.7	11
Bor + doxil vs Bor	44/27 41/19	9 6.5	76% at 15 mos 65% at 15 mos	12
Bor SQ vs Bor IV	52/25 52/25	10.2 8.0	72% at 12 mos 76% at 12 mos	13
Bor + Thal + Dex vs Thal + Dex	94/56 86/35	18.3 13.6	71% at 24 mos 65% at 24 mos	7
Bor/Dex/Panobinostat vs Bor/Dex	60/27 54/15	11.9 8	33 30	17
Bor/Vorinostat vs Bor	56/7.9 (CR) 40/5.3 (CR)	7.6 6.8	NA 28	18
Bor/Dex vs Carfilzomib/Dex	63/29 77/54	9.4 18.7	NA NA	16
Len/Dex vs Dex	60/24 24/5	11.3 4.7	NR 20.6	14, 15
Len/Dex vs Dex	61/24 20/2	11.1 4.7	29 20	
Len/Dex/Ixazomib vs Len/Dex	78/48 71/39	20 14	NA	8
Len/Dex/Elotuzumab vs Len/Dex	79/33 66/28	19 15	NA	9
Len/Dex/Carfilzomib vs Len/Dex	87/70 66/40	26 17	73% at 24 mos 65% at 24 mos	10

Notes: ^aMedian in months, except where noted.

Abbreviations: Bor, bortezomib; CR, complete remission; Dex, dexamethasone; IV, intravenous; Len, lenalidomide; mos, months; NA, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SQ, subcutaneous; Thal, thalidomide; VGPR, very good partial response; NR, not reported.

Table 2 Regimens for relapsed refractory multiple myeloma therapy based on Phase 1/2 clinical trials

Regimen	Trial	ORR% CR/VGPR%	PFS (months) ^a	OS (months) ^a	References
Bortezomib based	Bor ± Dex	34/10	7	10	48, 49
	Bor ± Dex	67/33			
	Bor + cytoxan + Dex	95/61	83% at 12 mos	100% at 12 mos	50
	Bor + Bendamustine + Dex	45/29	11.8	66% at 12 mos	51
Lenalidomide based	Len + Cytosan + Dex	81/36	56% at 24 mos	80% at 30 mos	52
	Len + Bor + Dex	63/20	7	16	53
	Len + Bendamustine + Dex	76/24	6.1	NA	54
	Car	24/5.5	7.8	15.6	55
Carfilzomib based (Car)	Car + Pom + Dex	50/16	7.2	20.6	40
	Car + Panobinostat + Dex	67/33	7.7	NA	42
	Car + Filanesib	30/NA	NA	NA	56
	Car + Selinexor + Dex	75/12.5	NA	NA	47
	Pom + Dex	33/3	4.2	16.5	57
Pomalidomide based					
Others	Daratumumab	36/9	5.6	77% at 12 mos	58
	VDT-PACE	63/7	7	NA	59

Notes: ^aMedian in months, except where noted.

Abbreviations: Bor, bortezomib; Car, carfilzomib; CR, complete remission; Dex, dexamethasone; Len, lenalidomide; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Pom, pomalidomide; Thal, thalidomide; VGPR, very good partial response; VDT-PACE, bortezomib, dexamethasone, thalidomide, cisplatin, adriamycin, cytoxan, etoposide.

Role of second autologous stem cell transplant

Autologous stem cell transplantation is often used as part of up-front therapy in younger patients and has been shown to improve both progression-free survival (PFS) and OS in multiple randomized trials.^{19,20} Although there have been no randomized trials comparing a second autologous stem cell transplantation to nontransplant therapy in relapsed/refractory scenario, it is sometimes offered to sufficiently fit patients. Center for International Blood and Marrow Transplant Research reported outcomes of 187 patients who underwent second autologous stem cell transplantation for relapsed myeloma, analyzed retrospectively.²¹ The overall response rate was 68% (with 25% of the patients achieving a CR), the median PFS was 11.2 months with a median OS of 30 months. Overall, the therapy was well tolerated with a nonrelapse mortality of 2% during the first year after second autologous stem cell transplant. Similar outcomes have been reported by other groups.^{22,23} In summary, for eligible patients, a second autologous stem cell transplant is an effective and safe therapy and comparable with other available therapies in this situation.

Pharmacology of carfilzomib and other proteasome inhibitors

Proteasome inhibitors have become one of the most widely used classes of drugs in the therapy of multiple myeloma. Bortezomib was the first proteasome inhibitor to be approved for this disease, first in relapsed disease and subsequently for up-front therapy. The proteasome is an enzymatic complex

required for intracellular degradation of proteins in all human cells.^{24,25} The functional unit named 26S proteasome complex is made of a 20S core catalytic complex that is capped at each end by a 19S regulatory subunit. There are three catalytic sites within the 20S core: β 1 (caspase-like), β 2 (trypsin-like), and β 5 (chymotrypsin-like). The proteasome is responsible for degradation of multiple cellular proteins including some proteins essential to the cell cycle, such as cyclins A, B, D, E, and cyclin-dependent kinase inhibitor,²⁶ tumor suppressor proteins such as p53²⁷ and also I- κ B, which is an inhibitor of NF- κ B pathway in plasma cells.²⁸ Dysregulation of such pathways via proteasome inhibition leads to cell apoptosis.²⁴

Bortezomib is a boron-containing proteasome inhibitor²⁵ that binds predominantly to the chymotrypsin-like site of the 20S proteasome, causing inhibition of its function. The binding is reversible and dose dependent.²⁹ Carfilzomib is derived from ketoepoxide compounds that are potent inhibitors of the proteasome, as well.³⁰ Carfilzomib also binds to the β 5 chymotrypsin-like subunit, but more specifically with regards to the other catalytic subunits compared with bortezomib. Also, the binding is irreversible.³¹ It is postulated that this subunit specificity may account for a lower incidence of certain side effects with carfilzomib, namely peripheral neuropathy. In preclinical studies,^{31,32} carfilzomib inhibited proliferation and activated apoptosis in myeloma cell lines more potently than bortezomib and displayed activity against bortezomib-resistant myeloma cell lines and samples derived from patients with bortezomib-resistant myeloma.³² In addition, Kuhn et al³² showed that in preclinical models, carfilzomib caused preferential inhibition of chymotrypsin-like

activity $\beta 5$ subunit of proteasome at concentration as low as 10 nM and had no effect on the trypsin-like activity of the $\beta 2$ subunit at concentrations as high as 100 nM.

In terms of pharmacokinetics after intravenous (IV) administration, carfilzomib is rapidly cleared from plasma, with the majority of drug eliminated from plasma within 30 minutes of administration.^{33,34} The drug is highly protein bound in the plasma. The rapid clearance of carfilzomib is primarily mediated by metabolism instead of renal excretion. The majority of the drug is metabolized and converted into inactive metabolites by extra hepatic metabolism.³⁴ The p-450 system plays only a minor role in metabolism of the drug. The excretion of the drug is mainly in the form of inactive metabolites.

The pharmacokinetics and safety of carfilzomib is similar in patients with poor renal function as compared to patients with normal renal function.³⁵ Thus, the drug can be safely used in patients with impaired renal function without dose reduction. Currently, carfilzomib is approved as a twice-weekly IV infusion on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle (20 mg/m² in cycle 1, week 1 and 27 or 56 mg/m² beyond). The drug is also approved using the same administration schedule at a dose of 27 mg/m² in combination with lenalidomide and dexamethasone.

Clinical studies in patients with relapsed multiple myeloma, with a focus on second-line use

On the basis of the excellent preclinical activity,^{31,32} carfilzomib was initially evaluated in two Phase 1 human studies.^{36,37} In the first study, the drug was administered on five consecutive days in a 14-day cycle and dose escalation proceeded from 1.2 to 20 mg/m². Twenty-nine patients with various hematologic malignancies were enrolled in the study and the maximum tolerated dose (MTD) was established at 15 mg/m² in this study. Dose limiting toxicities seen in the 20 mg/m² cohort consisted of febrile neutropenia and grade 4 thrombocytopenia. Pharmacodynamic studies revealed proteasome inhibition of >75% after a single dose of carfilzomib at dose levels of 15 mg/m² and higher. Clinical responses were seen in patients with multiple myeloma at doses >11 mg/m². Because of anticipated logistical difficulties related to prolonged therapy with dosing on 5 consecutive days every 2 weeks, a separate Phase 1 study was done to investigate twice-weekly schedule.³⁷

In the second Phase 1 study,³⁷ patients with multiple myeloma and lymphoma (N=48) were enrolled and treated with escalating doses of carfilzomib from 1.2 to 27 mg/m² with twice-weekly IV infusions on days 1, 2, 8, 9, 15, and 16

of a 28-day cycle. In this study, the MTD was not reached. Very few nonhematologic grade ≥ 3 adverse events (AEs) were seen. The common grade 1–2 nonhematologic AEs were gastrointestinal upset and fever. There was no documented grade 3+ peripheral neuropathy. The grade 3+ hematologic AEs observed were anemia and thrombocytopenia, each seen in ~27% of patients. Pharmacodynamic studies confirmed that doses of 15 mg/m² resulted in >80% proteasome inhibition in whole blood with very minimal recovery of proteasome activity seen between the doses of carfilzomib. Objective responses were seen both in multiple myeloma and non-Hodgkin's lymphoma and doses >15 mg/m² on this dosing schedule. On the basis of this study, this dosing schedule was chosen for evaluation in further trials.

On the basis of the above data, carfilzomib was evaluated in a Phase 2 study³⁸ of relapsed and refractory multiple myeloma patients at a dose of 20 mg/m² in the first cycle and then increased to 27 mg/m² in the subsequent cycles (20/27 mg/m²) along with dexamethasone 4 mg with each dose of carfilzomib. In this study, 95% of the 257 enrolled patients were refractory to their last therapy; 80% were refractory or intolerant to both bortezomib and lenalidomide. Patients had received a median of five lines of therapy prior to the study. The overall response rate in the study was 23.7% with a CR+VGPR rate of 14% and median duration of response 7.8 months in responding patients. In terms of the AEs, the most common grade ≥ 3 AEs were anemia and thrombocytopenia, each seen in ~25% of the patients, and also fatigue in ~8% of the patients. Dyspnea attributed to carfilzomib, usually transient, was seen in ~17% of patients. Renal dysfunction was seen in 25% of patients, with roughly two-thirds of cases felt to be related to carfilzomib therapy. Congestive heart failure was seen in 3.8% of patients. Finally, although worsening peripheral neuropathy was seen in 12.4% of patients, it was grade ≥ 3 in only 1.1% of patients.

Another Phase 2 study³⁹ evaluating the use of single-agent carfilzomib in bortezomib-naïve relapsed/refractory multiple myeloma patients showed somewhat better antimyeloma activity. The objective response rate (ORR) was 52% with a CR+VGPR rate of 19% in patients treated at a 20/27 mg/m² dose (N=70). The median number of earlier therapies was two in this study. AEs were similar to those seen in previous trials, including a low incidence of severe peripheral sensory neuropathy. Thus, as had been previously demonstrated with bortezomib,^{6,12,13} antimyeloma efficacy of carfilzomib seems to be higher when used in less heavily treated patients.

Two Phase 3 trials using carfilzomib-containing regimens in patients with multiple myeloma who have had 1–3

prior lines of therapy have been published. The ASPIRE trial¹⁰ compared lenalidomide/dexamethasone/carfilzomib with a control arm of lenalidomide/dexamethasone. A total of 792 patients were enrolled in the study. Patients had received a median of two prior lines of therapy, including ~65% of patients who had received bortezomib in the past. Carfilzomib was given at a dose of 20/27 mg/m² with lenalidomide 25 mg/day and dexamethasone 40 mg. The overall response rate in the experimental arm was 87% as compared to 67% in the control arm, and the likelihood of achieving a VGPR or better was 70% vs 40%. The median PFS was improved from 17 months in the control arm to 26 months in the experimental arm. Two-year OS was improved from 65% to 73% ($P=0.04$). Efficacy data for the 43% of enrolled patients who had had only one prior line of therapy (ie, were getting second-line therapy) was not specifically reported. Serious AEs were seen in 59% of patient in the experimental arm compared with 53% in the control arm. There was a slight excess of grade ≥ 3 dyspnea (2.8% vs 1.8%), renal dysfunction (3.3% vs 3.1%), congestive heart failure (3.8% vs 1.8%), ischemic heart disease (3.3% vs 2.1%), and hypertension (4.3% vs 1.8%) in the carfilzomib-containing arm.

The second Phase 3 trial, so called ENDEAVOR trial,¹⁶ compared carfilzomib (at a dose of 20 mg/m² on days 1, 2 of cycle 1, and 56 mg/m² subsequently) plus dexamethasone with bortezomib (1.3 mg/m² IV or subcutaneous [SQ] on days 1, 4, 8, and 11) plus dexamethasone in 929 patients. As in the ASPIRE trial, patients had all received between 1 and 3 prior lines of therapy. The preliminary results did show improvement in ORR (63% vs 77%), as well as the rate of achieving a VGPR or better (29% vs 54%). Furthermore, PFS was longer in the carfilzomib arm (18.7 months vs 9.4 months). There was a slight excess of grade 3+ anemia and hypertension in the carfilzomib arm, but the on-therapy deaths due to AEs for each arm was similar (4% for carfilzomib/dexamethasone vs 3% for bortezomib/dexamethasone).

Given these results, multiple other carfilzomib-containing combinations, including carfilzomib, pomalidomide and dexamethasone;⁴⁰ carfilzomib, cyclophosphamide and dexamethasone;⁴¹ and carfilzomib plus panobinostat⁴² have been explored. Table 2 highlights the details of these and other carfilzomib-containing regimens in relapsed multiple myeloma. In general, carfilzomib is given at a dose of 20/27–20/36 mg/m² when given according to a standard schedule, but the dose may be escalated if a weekly (rather than twice weekly) schedule is used. This will be discussed further in the following section.

Patient-focused perspectives, such as quality of life, patient satisfaction/acceptability, and adherence

The standard twice-weekly (for 3 out of 4 weeks each cycle) administration schedule carfilzomib can be somewhat onerous, particularly for patients receiving the drug over a long period of time. A common strategy to address this is to switch to an alternate-week schedule as “maintenance”, usually after 8–9 cycles of full-intensity therapy.⁴³ Using this approach, carfilzomib is administered on days 1, 2, 15, and 16 of each 4-week maintenance cycle. An alternative to this has been the development of weekly carfilzomib therapy. Escalated weekly dosing has been evaluated in a large Phase 1/2 study⁴⁴ in which an MTD of 70 mg/m² given once a week was established. The efficacy of the drug did not appear to be compromised; if anything, the higher dose weekly therapy was associated with an overall response rate of 77% – higher than the response rates in previous trials using standard dose and schedule. The frequency and severity of side effects observed in this trial were similar to previous reports involving standard dosing. As such, carfilzomib 70 mg/m² weekly is currently being compared with standard 20/27 mg/m² dosing twice-weekly in a randomized trial. It should be noted that doses of carfilzomib of 36 mg/m² or higher should be administered over 30 minutes, as opposed to the 2- to 10-minute infusion time used for lower doses.

The IV route of administration is an inconvenience, particularly as other approved proteasome inhibitors are administered either SQ (bortezomib) or orally (ixazomib). The oral proteasome inhibitor ixazomib has recently been approved in combination with lenalidomide plus dexamethasone for patients with relapsed multiple myeloma who have previously received one line of therapy. The pivotal Phase 3 trial, which led to the approval of ixazomib, did not include patients with bortezomib-refractory disease,⁸ leaving the question of the oral proteasome inhibitors efficacy in this group. Therefore, at this time, carfilzomib remains the proteasome inhibitor of choice in patients with bortezomib-refractory multiple myeloma. Efforts at developing oprozomib, an oral drug with structural similarities to carfilzomib, have met with difficulty, largely due to gastrointestinal toxicity. This has been observed in trials involving myeloma patients⁴⁵ and patients with solid tumors.⁴⁶

Health-related quality of life (QoL) was formally studied in the ASPIRE trial (carfilzomib, lenalidomide, dexamethasone vs lenalidomide, and dexamethasone).¹⁰ Two validated health-related QoL instruments (EORTC QLQ-C30 and QLQ MY20) were administered on day 1 of

cycles 1, 3, 6, 12, 18, and at the end of the treatment. The triplet therapy group had higher QLQ-C30 Global Health Status/QoL scores compared with doublet therapy over 18 cycles of treatment ($P < 0.0001$). In addition, there was no difference in terms of the impact of AEs on QoL between the two groups indicating no additive negative impact of triplet therapy (KRd) vs doublet therapy (Rd) in this trial.

Conclusions and future directions

Carfilzomib represents an important therapy for patients with relapsed/refractory multiple myeloma. Optimal dose and schedule is still being evaluated. It seems likely that higher doses (20/36–20/56 mg/m² when administered twice-weekly; 70 mg/m² when administered once-weekly) are associated with higher response rates without appreciable increases in toxicity. Combining carfilzomib with other agents is feasible and also generally improves efficacy compared with standard twice-weekly carfilzomib monotherapy. In general, inherent and acquired resistance to carfilzomib in relapsed myeloma is an issue even today. Recent work has focused on identifying and overcoming resistance mechanisms. For example, a recent trial adding the CRM-1 inhibitor selinexor to carfilzomib in patients with carfilzomib-refractory myeloma was undertaken after preclinical studies showed that selinexor may restore sensitivity to carfilzomib.⁴⁷ Furthermore, the role of carfilzomib in the setting of relapsed myeloma will likely evolve if the drug becomes approved for use as part of frontline therapy.

Disclosure

Dr Zonder is a consultant for Takeda, the manufacturer of bortezomib and ixazomib. The authors report no other conflicts of interest in this work.

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