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A clinical update on the role of carfilzomib in the treatment of relapsed or refractory multiple myeloma

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***Abstract*:** Even though the prognosis of patients with multiple myeloma is continuing to improve, all patients eventually develop relapsed refractory disease. Several novel therapeutics have been developed in the last few years including the second-generation proteasome inhibitor carfilzomib which has been approved for patients with relapsed and refractory multiple myeloma in the United States since 2012. Recently data from several phase III studies have become available showing the promising efficacy of carfilzomib in combination with lenalidomide, which led to the renewed approval of carfilzomib in combination with lenalidomide and dexamethasone for relapsed myeloma in 2015. Furthermore carfilzomib showed superiority over bortezomib on both efficacy and toxicity profiles, especially a profoundly lower incidence in polyneuropathy. Carfilzomib has been shown to partially overcome the negative effects of high-risk cytogenetics. Promising combinations of carfilzomib with histone deacetylase (HDAC) inhibitors, pomalidomide and several other novel therapeutics have been presented in early studies. The optimal dosing regimen and sequence of treatment regimens remain important questions for the future.

Keywords: myeloma, relapse, refractory, proteasome inhibitor, carfilzomib

Introduction

The outcome of patients with multiple myeloma (MM) has drastically improved over the last decade due to novel therapies like the immunomodulatory drugs lenalidomide and thalidomide and the proteasome inhibitor bortezomib [Kumar *et al.* 2014]. However, all patients eventually develop relapsed and refractory disease, after which their prognosis is very poor as shown by Kumar and colleagues. In their cohort of 286 patients, all refractory to bortezomib and refractory to, progressive on, or intolerable to lenalidomide, the median overall survival (OS) was only 9 months [Kumar *et al.* 2012]. Carfilzomib is a new proteasome inhibitor which, in contrast to the reversible binding of bortezomib, binds irreversibly and selectively to its target: the chymotrypsin-like activity of the 20S proteasome. By inhibiting proteasome function it stops proteolysis leading to accumulation of intracellular proteins and apoptosis. In the United States, carfilzomib has been approved for the treatment of patients with MM who are refractory to, or have relapsed on one to three previous therapies. In the last year the results of the first phase III trials testing carfilzomib have been presented. Also several new combination therapies including carfilzomib have been tested in phase I/II studies. Here we review the mechanism, efficacy and safety of this novel therapeutic in the treatment of relapsed or refractory MM (RRMM), including the most recent studies.

Mechanism of action, pharmacokinetics and pharmacodynamics

The ubiquitin–proteasome pathway has an important regulatory role in the cell cycle [Coux *et al.* 1996; Hershko and Ciechanover, 1998]. Its main function is tagging damaged and misfolded proteins with ubiquitin which leads them to the proteasome for degrading. This process has an important role in key intracellular processes like protein degradation, regulation of cell cycle, apoptosis and DNA repair [Niewerth *et al.* 2014]. Proteasome inhibition leads to intracellular accumulation of unfolded proteins, inhibition of

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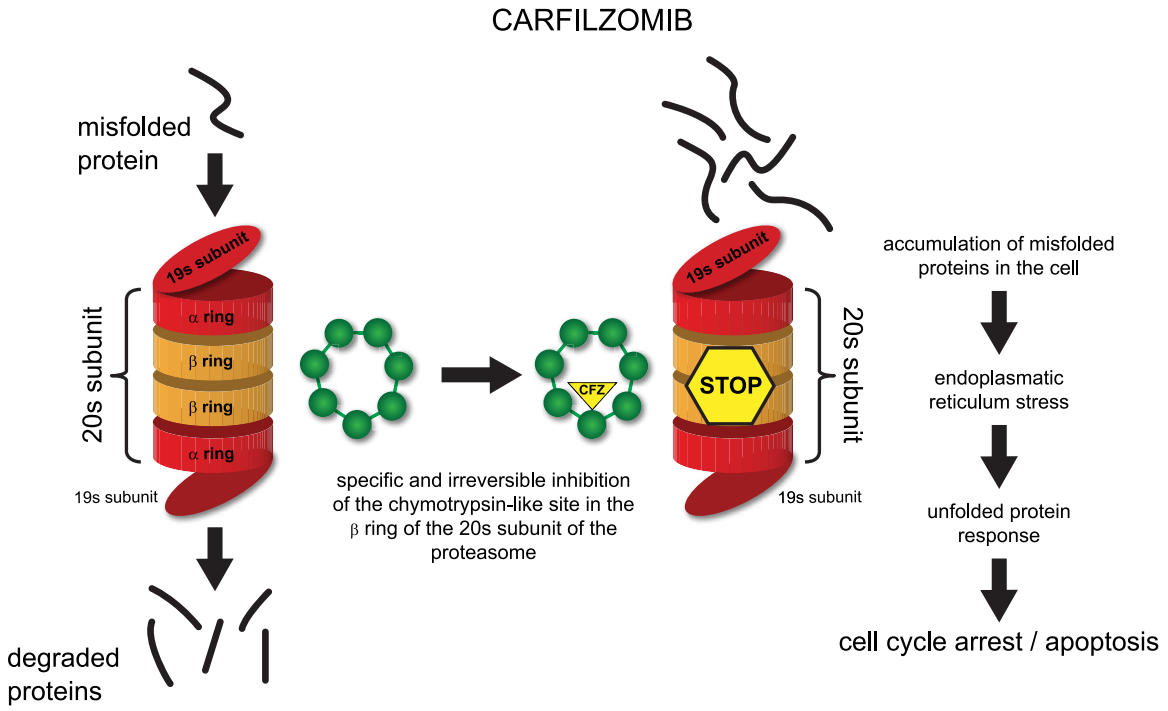

Figure 1. Mechanism of proteasome inhibition by carfilzomib (image provided by Amgen).

nuclear factor κB and eventually apoptosis. Plasma cells produce large quantities of protein and are therefore highly susceptible to proteasome inhibition [Obeng *et al.* 2006; Hideshima *et al.* 2002]. The 26S proteasome consists of a 20S core between two 19S cap complexes. The 20S core is made up of two identical rings of seven α subunits and two identical rings of seven β subunits. Ubiquinated proteins are recognized by the 19S complex and thereafter guided to the 20S core where the α subunits are responsible for recognizing and unfolding the ubiquinated protein. There are three catalytically active β subunits: β1 (caspase like), β2 (trypsin like) and β5 (chympotrypsin like) which are responsible for protein degrading. The β5 subunit has been shown to be the rate limiting step in proteolysis. Its inhibition is the most effective in hindering cellular growth, however coinhibition of other proteolytic sites has been shown to increase the inhibitory effect [Rock *et al.* 1994]. Carfilzomib is a proteasome inhibitor that binds relatively selectively to the β5 subunit exhibiting chymotrypsin-like activity and in higher concentrations also inhibits the subunits with trypsin-like activity. In contrast to bortezomib, its binding is irreversible [Demo *et al.* 2007; Parlati *et al.* 2009]. Furthermore, bortezomib also binds to a multitude of other proteases due to its different structure. *In vitro* studies have shown that inhibition of other proteases by bortezomib leads to neurodegradation whereas carfilzomib had no such effect. This may explain why the nonselective binding of bortezomib seems to play an important role in the high rates of sensory polyneuropathy associated with this drug [Arastu-Kapur *et al.* 2011].

Carfilzomib has a good penetration throughout the body but does not cross the blood–brain barrier. It has a very short half life of approximately 30 min and is metabolized extrahepatically into nonactive metabolites. This means carfilzomib is not dependent on liver function and interactions with hepatically cleared comedication, in contrast to bortezomib which is mostly metabolized in the liver [Wang *et al.* 2011; Yang *et al.* 2011]. The inhibition of proteasome function by carfilzomib in peripheral blood mononuclear cells was measured 1 h after administration in several phase I studies. Alsina and colleagues showed up to 70% inhibition at 15 mg/m^2 and up to 90% inhibition at 27 mg/m^2. On the second day of administration there was no recovery of proteasome function prior to the carfilzomib dose and similar or further inhibition of proteasome function after the second dose [Alsina *et al.* 2012]. O'Connor and colleagues showed up to 90% of inhibition dosing on five consecutive days at a maximum of 20 mg/m^2.

Both studies showed recovery of proteasome function at the start of a second complete cycle [O'Connor *et al.* 2009]. Mechanisms of resistance have been more thoroughly examined for bortezomib [Niewerth *et al.* 2015] and include the mutation or amplification of proteasomal subunits, alterations in endoplasmic reticulum (ER) stress response, upregulation of autophagy as an alternative for protein degrading, overexpression of the vesicle membrane protein myristoylated alanine-rich C-kinase substrate (MARCKS) and alterations in the bone marrow microenvironment. Since carfilzomib is able to overcome bortezomib resistance it is unlikely that resistance mechanisms for both drugs are identical. Data on the resistance mechanisms of carfilzomib are limited, however the upregulation of the multidrug efflux transporter MDR1/P-glycoprotein (Pgp/ABCB1), whose role in bortezomib resistance is arbitrary, induced carfilzomib resistance in *in vitro* studies. Inhibitors of Pgp seem to overcome this resistance [Obeng *et al.* 2006].

Use of carfilzomib monotherapy in patients with RRMM

Initial pharmacokinetics and toxicity of carfilzomib were investigated in two phase I studies. PX-171-001 dosed carfilzomib on days 1–5, every 14 days. The maximum tolerated dose (MTD) was 15 mg/m^2 due to grade 3 febrile neutropenia and grade 4 thrombocytopenia. In PX-171-002 an alternative dosing regimen was used on days 1, 2, 8, 9, 15 and 16 every 28 days. The MTD was not reached in this study but the maximum tested dose was 27 mg/m^2. The most common grade 3 and 4 adverse events (AEs) were anemia and thrombocytopenia. Promising was that only 14% of patients developed treatment-related neuropathy and that none of these cases were grade 3 or 4 [Alsina *et al.* 2012; O'Connor *et al.* 2009].

The PX-171-003-A1 study was the first phase II study to evaluate overall response rate (ORR) on carfilzomib in patients with RRMM. Due to its tolerability, the maximum tolerated dosing regimen from the PX-171-002 study was used. A total of 257 patients were evaluable for efficacy. Patients were heavily pretreated with a median of five prior therapies including bortezomib (99.6%), lenalidomide (94%) and thalidomide (75%). Ninety-five percent of patients were refractory to their last treatment and 80% of patients were intolerant to or refractory on both bortezomib and lenalidomide. ORR was 23.7%, median progression free survival (PFS) was 3.7 months, median duration of response (DOR) was 7.8 months. The OS rate of 15.6 months in this cohort was an important improvement compared with the 9-month OS in the previously mentioned bortezomib and lenalidomide refractory cohort studied by Kumar and colleagues [Kumar *et al.* 2012]. Most grade 3/4 AEs were hematological and well manageable. The promising results of this study in this heavily pretreated double refractory population led to the accelerated approval of carfilzomib [Siegel *et al.* 2012].

Further phase II testing was reported in the PX-171-004 trial, which evaluated carfilzomib in bortezomib-naive patients with RRMM with a median of two prior therapies. A total of 129 patients received carfilzomib on days 1, 2, 8, 9, 15 and 16 in a 28-days cycle. The first cohort of 59 patients received a dose of 20 mg/m^2. A second cohort of 70 patients escalated to 27 mg/m^2 at cycle 2 after an amendment due to the results of the PX-171-002 study. The ORRs were higher than in the previous studies with bortezomib-refractory patients and were 42.2% and 52.2% in cohort 1 and 2 respectively. Median duration of response was 13.1 months for cohort 1 and not reached for cohort 2 and PFS was 8.3 months and not reached. All of these results were also higher than in bortezomib-refractory patients. AEs were comparable with previously reported rates at the same dose levels. The study showed that single agent carfilzomib is even more effective in patients who are bortezomib naïve than patients with RRMM who have received bortezomib, with similar toxicity [Vij *et al.* 2012].

In all previous studies mentioned above the infusion time of carfilzomib was 2–10 min. Papadopoulos and colleagues confirmed the apparent safety of a dose-escalation regime when they examined MTD, pharmacokinetics and pharmacodynamics in a phase I dose-escalation study with an infusion time of 30 min with a similar dosing cycle as in the PX-171-002 study. An important finding from this study was that the prolonged infusion time seemed to increase the MTD to 56 mg/m^2 compared with a previously maximum tested dose of 27 mg/m^2 in PX-171-002. Furthermore, although the cohort was much smaller, the ORR was more than doubled to 50% compared with PX-171-003-A1 where it was 23.7%. Nausea, dyspnea and fatigue were the most common AEs but the vast majority were

grade 1 and 2 events and most grade 3/4 events were hematological at slightly higher rates than reported in earlier studies. Higher doses were well tolerated if infusion time was prolonged to 30 min, with increased efficacy and only slightly increased but well manageable toxicity [Papadopoulos *et al.* 2015].

In the phase III FOCUS trial 315 patients with RRMM were randomized between single agent carfilzomib and low-dose steroids with or without continuous low-dose oral cyclophosphamide. All patients were previously treated with bortezomib, lenalidomide, corticosteroids and an alkylating agent. A total of 61.8% and 63.3% of patients were bortezomib and lenalidomide refractory in the carfilzomib and control group respectively. Carfilzomib was administered in a 28-day cycle, similar to the dosing regimen in the PX-171-003-A1 study at 20/27 mg/m^2. The control arm received 30 mg oral prednisone, 6 mg oral dexamethasone or a similar steroid every other day. The addition of 50 mg oral cyclophosphamide to the control group was optional, however 94.8% of patients received this additional therapy. In contrast to the promising results of earlier phase I/II studies, the primary endpoint of OS was not met: in the carfilzomib group, it was 10.2 months compared with 10.0 months ($p = 0.42$) in the control group. On the secondary endpoint of response rate there was a slight difference in favor of carfilzomib (19.1% *versus* 11.1%; $p = 0.03$). However, this was not translated into an increase in PFS, which was 3.7 and 3.3 months for the carfilzomib and control group respectively ($p = 0.25$). AEs were similar to those reported in previous phase I/II studies with the exception of higher rates of renal failure: 17.2% of grade 3 and higher renal failure in the carfilzomib group *versus* 5.2% in the control group. Although the rates of cardiac failure (4.5%) were similar to those reported in phase I/II studies, the difference in the control group (0.7%) is striking, suggesting that carfilzomib may have cardiac toxic effects as discussed below. The failure of the study to meet its primary endpoint was probably due to the high efficacy of additional cyclophosphamide treatment in the control group. The addition of cyclophosphamide to standard chemotherapy, thalidomide, bortezomib and most recently lenalidomide has increased response rates, sometimes dramatically, as seen in the response rate of 81% after addition to lenalidomide and prednisone in lenalidomide/dexamethasone (Rd) refractory patients [Kropff *et al.* 2007; Sidra *et al.* 2006; Schey *et al.* 2010; Ludwig *et al.* 2014; Donk *et al.* 2010].

Combination therapy

Lendvai and colleagues performed a phase II study of 56 mg/m^2 carfilzomib with the possibility of adding dexamethasone in 44 patients with RRMM. Patients were pretreated with a median of five prior regimes, including at least one regimen with bortezomib; 55% achieved at least a partial response (PR). PFS, DOR and OS were 4.1, 11.7 and 20.3 months respectively. Thirty-five patients reached the per-protocol population for efficacy analysis. Noteworthy is that 4 out of 11 patients who received dexamethasone in addition to carfilzomib because of failed response still achieved a PR or better [Lendvai *et al.* 2014]. The phase I/II CHAMPION-1 trial explored a different dosing regimen, with carfilzomib being administered in a once weekly schedule. Patients received carfilzomib on days 1, 8 and 15 in a 28-day cycle, with 40 mg dexamethasone given on days 1, 8, 15 and 22. MTD was established at 70 mg/m^2 with an ORR of 77%. Median PFS was 12.6 months. In comparison to other trials, patients were not as heavily pretreated. The median number of previous therapies was only one and 52% of patients were bortezomib refractory. AEs were comparable to the twice weekly schedule.

The weekly 20/70 mg/m^2 dose is currently being compared with the standard 20/27 mg/m^2 approved dosing schedule in a phase III trial [Berenson *et al.* 2016].

Carfilzomib/dexamethasone versus *bortezomib/dexamethasone*

The ENDEAVOR study was the first and to date only phase III trial comparing the two proteasome inhibitors carfilzomib and bortezomib. A total of 929 patients with RRMM were randomized between carfilzomib (20/56 mg/m^2)/dexamethasone (20 mg; Kd) and bortezomib (1.3 mg/m^2 subcutaneously or intravenously)/dexamethasone (20 mg; Vd). The median number of prior therapies was two, with 54% of patients pretreated with bortezomib in both groups. The primary endpoint was PFS, which was doubled in the Kd group (18.7 *versus* 9.4 months; HR 0.53; $p < 0.0001$). ORR was also significantly higher (77% *versus* 63%; OR 2.01; $p < 0.0001$) in the Kd group and the number of patients who achieved a minimum

complete response (CR) (13% *versus* 6%; $p = 0.001$) and minimum Very Good Partial Remission (VGPR) (54% *versus* 29%; $p < 0.0001$) almost doubled. Furthermore the DOR was also doubled (21.3 *versus* 10.4 months). A difference in OS was probably not found due to the relative short follow up, however a trend in favor of Kd was seen. Since neuropathy is one of the most common and incapacitating side effects of bortezomib it was even more promising to see that the rate of polyneuropathy in the carfilzomib group was only a third of that in the bortezomib group (9% *versus* 27%; odds ratio 0.14; $p < 0.0001$). Rates of diarrhea and constipation were also far lower in the carfilzomib group; only rates of hypertension, dyspnea and pyrexia were higher but were mostly grades 1 and 2. Overall the study showed superior efficacy of carfilzomib over the first-generation proteasome inhibitor bortezomib with a far more favorable toxicity profile most importantly on polyneuropathy [Dimopoulos *et al.* 2016].

Carfilzomib, lenalidomide, dexamethasone

The phase IB/II PX-171-006 study was the first study in which carfilzomib was combined with the immunomodulator lenalidomide and dexamethasone and included a total of 84 patients with RRMM. In the phase I dose-escalation part the maximum planned dose (MPD) was established as well tolerated (carfilzomib 20/27 mg/m^2 days 1, 2, 8, 9, 15 and 16, lenalidomide 25 mg days 1–21, dexamethasone 40 mg days 1, 8 and 15 in a 28-day cycle) [Niesvizky *et al.* 2013]. The phase II part of the study focused on the 52 patients treated at the MPD. ORR was 76.9% for the MPD group and 69.0% for the total cohort. PFS was 15.4 and 11.8 months respectively. In the MPD cohort the bortezomib-refractory patients reached ORR of 69.2%, while for the lenalidomide-refractory patients this was 69.9%. DOR were 22.1 and 10.8 months respectively. Data for double-refractory patients were not reported. Grade 3 and 4 AEs were mostly hematological in nature. The response rates in the lenalidomide refractory group suggest that addition of carfilzomib to lenalidomide may partially overcome lenalidomide resistance [Wang *et al.* 2013].

These results were the basis for further investigation in the phase III ASPIRE trial in which 792 patients with RRMM were randomized between carfilzomib/lenalidomide/dexamethasone (KRd) and Rd. The KRd dosing was similar as in the phase II trial. Patients who were previously progressive under bortezomib were excluded. Lenalidomide-pretreated patients were eligible provided it had not been their last therapy, their disease had not progressed within 3 months of starting lenalidomide therapy and they were not intolerable to it. Of all patients, 65.8% had previously been treated with bortezomib and 19.8% with lenalidomide. Other previous treatment regimens were not specified, with a median of two previous treatment regimens. An interim analysis was planned after 420 events and if the primary endpoint of PFS was met, secondary endpoints would be analyzed. Data from the interim analysis showed a significant difference for PFS of 26.3 months for the KRd group *versus* 17.6 months for the Rd group [hazard ratio (HR) 0.56; $p = 0.0001$]. OS was not reached in both groups. The response rate for KRd was higher at 87.1% *versus* 66.7% in the Rd group ($p < 0.0001$), with an impressive 31.8% reaching a complete response in the KRd group *versus* 9.3% in the control group ($p < 0.0001$). ORR in the KRd group was higher than the 69.0% reached in the previous phase II study. However, the latter study included more heavily pretreated patients, including more bortezomib (25%) and lenalidomide (44.2%) refractory patients. Furthermore only 26.9% of patients in the phase II trial were lenalidomide naïve compared with over 80% in this trial. AEs of grade 3 or higher were reported in 83.7% in the KRd group and 80.7% in the control group. Grade 3 and 4 events of interest that were more frequent in the KRd group were cardiac failure (3.8% *versus* 1.8%), ischemic heart disease (3.3% *versus* 2.1%), and hypertension (4.3% *versus* 1.8%). The rate of renal failure was comparable between the two treatment groups. Only 3.3% of patients developed grade 3 or higher renal failure in the KRd group, which is drastically lower than the 17.2% reported in the FOCUS trial [Stewart *et al.* 2015]. The results of this study led to the approval of the KRd regimen in the United States for patients with relapsed MM who received one to three prior therapies in 2015.

New combinations

Carfilzomib, pomalidomide, dexamethasone

In view of the successful KRd regimen, the combination of carfilzomib with the new immunomodulatory agent pomalidomide and dexamethasone was recently tested in 32 patients with RRMM in a phase I dose-escalation study. The MTD was set at dose level one (carfilzomib

20/27 mg/m^2 on day 1, 2, 8, 9, 15 and 16, pomalidomide 4 mg on day 1–21 and dexamethasone on day 1, 8 and 15). The ORR was 50%, which is slightly lower than in the KRd regimen. However, patients in this study were far more heavily pretreated, with a median of six prior therapies, and all were refractory to lenalidomide and all but two to bortezomib. The median PFS and OS were 7.2 and 20.6 months respectively. AEs were mostly hematological in nature and the rates were comparable with the KRd combination [Shah *et al*. 2015].

Carfilzomib with HDAC inhibitors and other new combinations

The combination of an HDAC inhibitor and a proteasome inhibitor has a synergistic effect by disrupting protein degradation by simultaneously disrupting proteasome and aggresome pathways *in vitro* [Hideshima *et al.* 2011]. HDAC inhibitors combined with bortezomib improved PFS in patients with RRMM in a number of phase III studies [Dimopoulos *et al.* 2013; San-Miguel *et al.* 2014]. Several phase I/II studies examined the combination of carfilzomib and a HDAC inhibitor. Three combined carfilzomib with panobinostat in RRMM. Berdeja and colleagues included 13 patients in the phase I part with panobinostat three times a week added to carfilzomib in week 1 and 3. Both of the studied medications were administered at the MPD (30 mg for panobinostat, 20/45 mg/m^2 for carfilzomib). The phase II part included an additional 31 patients. The ORR was 67%. Median time to progression and PFS were both 7.7 months. Median OS was not reached. Grade 3–4 toxicities were mostly hematological, with 59% of patients requiring dose reductions of panobinostat. These reductions led to the resolving of these toxicities in the following weeks of therapy [Berdeja *et al.* 2015]. Shah combined carfilzomib with panobinostat in a combination in which panibostat was added during the first 2 weeks of the carfilzomib cycle. A MTD was not reached with carfilzomib at a dose level of 20/45 mg/m^2 and panobinostat at 20 mg. ORR was 35% [Shah *et al.* 2012]. Kaufmann and colleagues added panobinostat to carfilzomib three times a week during the first 3 weeks of the 4-week carfilzomib cycle, which led to an ORR of 50% [Kaufmann *et al.* 2014]. Toxicity in all these studies were mostly hematological in nature and well manageable, but led to panobinostat dose reductions in 59% of patients in the study by Berdeja and colleagues, which included a panobinostat dose of 30 mg compared with 20 mg in the other studies. This suggests that the latter is a more tolerable dose. Other reported grade 3–4 toxicities were renal failure and pneumonia, but these were all well manageable. In another phase I study, vorinostat was added to the KRd regimen. It led to an ORR of 53% but with more (mostly hematological) grade 3 and 4 AEs then in the KRd regimen [Vesole *et al.* 2015]. More studies combining carfilzomib and HDAC inhibitors are needed to determine the role of this combination in the treatment of patients with RRMM. A phase Ib study combining carfilzomib at 20/36 mg/m^2 and ibrutinib at 560 mg or 840 mg showed an ORR of 58% with no new toxicities or severity of toxicities [Chari *et al.* 2015]. Further phase I/II studies with promising combinations of carfilzomib with novel therapeutics like the kinesin spindle protein inhibitor filanesib and the selective inhibitor of nuclear export selinexor have been presented recently [Jakubowiak *et al.* 2015; Zonder *et al.* 2015; Shah *et al*. 2015]. In figure 1 an overview is given of completede studies of Carfilzomib in RRMM.

Safety

AEs reported in studies using carfilzomib differ from the AEs known to be caused by bortezomib. The explanation probably lies in the more selective binding of carfilzomib to the proteasome. A pooled analysis of AEs in the main four phase II studies investigating single agent carfilzomib was performed by Siegel and colleagues [Siegel *et al.* 2013]. A total of 526 heavily pretreated patients with RRMM were analyzed who received carfilzomib at a maximum dose of 27 mg/m^2 on days 1, 2, 8, 9, 15 and 16. The most common AEs were anemia (46.8%), fatigue (55.5%) and nausea (44.9%), but the vast majority of these were grade 1 and 2 events. The most common grade 3 and 4 AEs were hematological in nature and were mostly reversible and well manageable. In total, 70.3% of patients experienced any hematological AE, but only 1.1% of patients required dose reduction because of this. Febrile neutropenia was reported in 1.1% of patients. Further trials showed similar hematological toxicity profiles. The most common infectious complications across trials were respiratory infections and pneumonia.

Polyneuropathy

Peripheral sensory polyneuropathy is a common problem in MM. Up to 75% of patients develop treatment-related polyneuropathy, especially those treated with bortezomib and thalidomide

[Richardson *et al.* 2012; Mohty *et al.* 2010]. Mileshkin and colleagues reported an incidence of 41% in patients treated with thalidomide [Mileshkin *et al.* 2006]. Moreau and colleagues showed that subcutaneous administration of bortezomib lowered the incidence of polyneuropathy but still reported 38% of patients developing polyneuropathy of any grade and 24% grade 2 or higher, making this an ongoing important problem [Moreau *et al.* 2011]. All studies performed with carfilzomib showed a far lower incidence of polyneuropathy. In the pooled analysis of Siegel and colleagues (Siegel et al. 2013), 84.8% of 526 patients had a history of polyneuropathy at baseline. In 71.9% of these patients this was still active, with all cases being grade 1 and 2. In total, 41 (13.7%) polyneuropathy-related AEs were reported. Only seven were grade 3 in patients who already had grade 1 or 2 polyneuropathy at baseline. The ENDEAVOR trial comparing carfilzomib and bortezomib showed a dramatic difference in the incidence of polyneuropathy in favor of carfilzomib (9% *versus* 27%), with similar incidences at baseline [Dimopoulos *et al.* 2016]. In the earlier mentioned phase III ASPIRE trial there were no differences in the incidence of polyneuropathy in the KRd and Rd groups [Stewart *et al.* 2015].

Cardiac toxicity

Cardiac risk factors or cardiovascular events are common in patients with MM [Kistler *et al.* 2012]. The earliest carfilzomib studies showed high incidences of dyspnea (42.2%) and cough (26.0%), for which a liberal hydration regimen was prescribed due to fear of tumor lysis syndrome. Although tumor lysis was uncommon, many cases of dyspnea were attributed to fluid overload and therefore cardiac related. The vast majority of cases of dyspnea in the cross-trial safety analysis resolved spontaneously without any additional measures, and dose reductions for dyspnea were rare [Siegel *et al.* 2013]. In the same analysis cardiovascular events in history were reported in 70.0% and 73.6% of patients at baseline. Cardiovascular AEs during the study were reported in 22.1%. Most of these (14.3%) were cases of hypertension, of which the majority were grade 1 or 2. In 7.2% of patients, congestive heart failure, pulmonary edema or decreased cardiac ejection fraction were reported, regardless of causality. Ischemic heart disease occurred in 3.4% of patients but of all patients with congestive heart failure or ischemic heart disease, the vast majority of 87% and 89% respectively had cardiac comorbidity. Cardiac-related AEs led to a dose reduction in six patients and discontinuation in 23 patients (4.4%). The events leading to discontinuation were congestive heart failure (1.5%), cardiac arrest (1.0%) and myocardial ischemia (0.6%). There was no difference in mortality between patients with or without cardiac risk factors in phase II studies [Siegel *et al.* 2013]. Congestive heart failure (6% *versus* 4%) and ischemic heart disease (6% *versus* 5%) were slightly more common in the KRd group then in the Rd group in the ASPIRE trail, however the incidence in the KRd group was comparable with the data presented in the single-agent studies [Stewart *et al.* 2015]. Furthermore, the overall rate of cardiac failure in the early phase II and III trials was similar to the rate reported in patients treated with bortezomib (8%) [Wang and Cheng, 2013]. However, a subanalysis of cardiac toxicity in the ENDEAVOR trial did show a substantial difference in cardiac toxicity between the carfilzomib and bortezomib groups. Serial echocardiography was performed to monitor cardiac function in 151 patients. Kd patients had higher incidences of heart failure (10.8% *versus* 4.1%) and hypertension (20.3% *versus* 8.1%), but a decrease in left ventricular ejection fraction (LVEF) in the first 24 weeks was not seen in any of the Kd patients and only one Vd patient. In total, an additional three patients (two Kd, one Vd) had decreased LVEF, all of which were reversible. This shows that screening with echocardiography to identify patients at risk of cardiac toxicity is not useful [Russel *et al.* 2015]. One study demonstrated a possible correlation between dose and cardiac toxicity, although the patients on higher doses were more heavily pretreated. Noteworthy is that this study showed no correlation between pre-existing cardiac conditions and incidence of toxicity [Land *et al.* 2015]. Several other small studies showed a rise in NT-proBNP shortly after carfilzomib treatment, however a correlation between LVEF and carfilzomib could not be found in these studies. Measurements of troponin after carfilzomib treatment showed an increase in a small number (2 out of 25) of patients, who both had pre-existing cardiac conditions [Rosenthal *et al.* 2014]. Overall there seems to be an increase in cardiac toxicity in an average of about 5% of patients, in which congestive heart failure appears to be the largest problem. Pathophysiological mechanisms remain unclear, however more heavily pretreated patients seem to be more at risk. Pre-existing cardiac conditions might also be a risk factor even though the results differ between

Table 1. Overview of completed studies evaluating carfilzomib in RRMM.

Study	Phase	Patients	ORR (%)	CR + VGPR (%)	PFS (months)	OS (months)
PX-171-003-A0 (carfilzomib monotherapy) [Jagannath *et al.* 2012]	IIB	46	16.7	0	3.5	NR
PX-171-003-A1 (carfilzomib monotherapy) [Siegel *et al.* 2012]	II	266	23.7	5.5 (0.4 + 5.1)	3.7	15.6
PX-171-004 (carfilzomib monotherapy, 20 mg/m^2 *versus* 27 mg/m^2) [Vij *et al.* 2012]	II	129	42.2 *versus* 52.2	17 (3.4 + 13.6) *versus* 28.4 (1.5 + 26.9)	8.2 *versus* NR	NR
PX-171-005 (carfilzomib monotherapy in renal dysfunction) [Badros *et al.* 2013]	II	50	25.5	0	NR	NR
PX-171-006 (carfilzomib + Rd) [Niesvizky *et al.* 2013]	IB	40	62.5	35 (2.5 + 32.5)	10.2	NR
PX-171-006 (carfilzomib + Rd) [Wang *et al.* 2013]	II	52	76.9	42.2 (5.7 + 36.5)	28.7	37
CHAMPION-1 (carfilzomib, 20/70 mg/m^2) [Berenson *et al.* 2016]	I/II	104	77	NR	12.6	NR
ENDEAVOR (Kd *versus* Vd) [Dimopoulos *et al.* 2016]	III	919	77 *versus* 63	54 (13 + 41) *versus* 29 (6 + 23)	18.7 *versus* 9.4	NE *versus* 24.3
FOCUS (carfilzomib *versus* best supportive care) [Ludwig *et al.* 2014]	III	315	30 *versus* 18	6 *versus* 5	3.7 *versus* 3.3	10.2 *versus* 10.0
ASPIRE interim analysis (carfilzomib + Rd *versus* Rd) [Stewart *et al.* 2015]	III	792	87.1 *versus* 66.7	69.9 (31.8 + 38.1) *versus* 40.4 (9.3 + 31.1)	26.3 *versus* 17.6	NR
Carfilzomib + pomalidomide + dexamethasone [Shah *et al.* 2015]	I/II	32	50	16 (0 + 16)	7.2	20.6
Carfilzomib + panobinostat [Berdeja *et al.* 2015]	I/II	42	67	33	7.7	NR
Carfilzomib + panobinostat [Shah *et al.* 2012]	I	17	35	12 (0 + 12)	NR	NR
Carfilzomib + panobinostat [Kaufman *et al.* 2014]	I	20	50	20	14.3	NR
Carfilzomib + Rd + vorinostat (QUAD) [Vesole *et al.* 2015]	I	17	53	12 (0 + 12)	12	NR
Carfilzomib *versus* carfilzomib + filanesib [Jakubowiak *et al.* 2015]	II	50	10 *versus* 30	NR	NR	NR
Carfilzomib + selinexor + dexamethasone [Zonder *et al.* 2015]	I	8	75	NR	NR	NR
Carfilzomib + Ibrutinib	I	40	58	NR	NR	NR

Kd, carfilzomib/dexamethasone; NR, not reported; Rd, lenalidomide/dexamethasone; RRMM, relapsed or refractory multiple myeloma; Vd, bortezomib/dexamethasone.

Table 2. Overview of adverse events reported in carfilzomib trials in patients with refractory and relapsed disease.

	Single agent, integrated safety profile (N = 526)		ENDEAVOR Kd (N = 463)		ENDEAVOR Vd (N = 456)		ASPIRE KRd (N = 392)		ASPIRE Rd (N = 389)	
	All grades (%)	>Grade 3 (%)	All grades (%)	>Grade 3 (%)	All grades (%)	>Grade 3 (%)	All grades (%)	>Grade 3 (%)	All grades (%)	>Grade 3 (%)
Hematological										
Anemia	46.8	22.4	39	14	27	10	42.6	17.9	39.8	17.2
Thrombocytopenia	36.3	23.4	21	9	17	9	29.1	16.6	22.2	16.3
Nonhematological										
Fatigue	55.5	7.6	29	5	28	7	32.9	7.7	30.6	6.4
Nausea	44.9	1.3	19	1	18	<1	–	–	–	–
Diarrhea	32.7	1	30	3	38	7	42.3	2.8	33.7	4.1
Constipation	20.9	0.2	14	<1	27	2	20.2	0.3	17.2	0.5
Dyspnea	34.6	4.9	28	5	11	2	19.4	2.8	14.9	1.8
Cough	26	0.2	25	0	14	<1	28.8	0.3	17.2	0
Pyrexia	30.4	1.7	28	2	14	<1	28.6	1.8	20.8	0.5
Any renal AE	9.1	5.5	8	4	4	2	8.4	3.3	7.2	3.1
Any cardiac AE	12.3	7.6	18	7	5	3.5	12.3	7.1	8.7	3.9
Headache	27.6	1.3	17	<1	10	<1	–	–	–	–
Hypertension	14.3		25	9	9	3	14.3	4.3	6.9	1.8
Pneumonia	12.7	10.5	9	7	10.5	8	–	–	–	–
Upper respiratory tract infection	28.3	3.2	20	2	15	<1	28.6	1.8	19.3	1
Peripheral neuropathy	13.9	1.3	19	2.2	51	8.3	17.1	2.6	17	3.1
Muscle spasms	–	–	18	<1	6	<1	26.5	1	21.1	0.8

AE, adverse event; Kd, carfilzomib/dexamethasone; KRd, carfilzomib/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone.

studies. Screening patients with measurements of NT-proBNP and echocardiography does not seem predictive and is therefore not recommended. There are limited data on the treatment of patients at risk or with a history of thromboembolism. In the ASPIRE trial the incidence of deep vein thrombosis was reported in 6.6% of the KRd group and 3.9% of the Rd group. All patients received prophylaxis for thrombosis [Stewart *et al.* 2015].

Renal impairment

Renal impairment is a common and serious complication in patients with MM [Bladé *et al.* 1998; Knudsen *et al.* 2000]. The safety and efficacy of single-agent carfilzomib in patients with RRMM and renal impairment was specifically tested in the phase II PX-171-005 study, which stratified patients by creatinine clearance (CrCl) (>80 ml/min, 50–80 ml/min, 30–49 ml/min, and <30 ml/min). Patients started at a dose of 15 mg/m^2 and if possible escalated to a 20/27 mg/m^2 regimen. There were no differences in carfilzomib exposure and clearance between the different groups. Incidence of grade 3–4 AEs was comparable to other phase II studies, and there were no differences in AEs between groups. Carfilzomib was safely escalated to 27 mg/m^2. The study showed that the safety and pharmacokinetics of carfilzomib do not seem to be affected by the degree of baseline renal impairment and that dose adjustments due to renal impairment are not necessary [Badros *et al.* 2013]. In the cross-phase II studies safety analysis, 23.8% of patients had moderate to severe renal impairment (CrCl < 50 ml/min) and 39.4% had mild renal impairment (CrCl 50–80 ml/min). Of the 515 patients evaluable for creatinine values, 86.8% did not have deterioration of renal function during treatment. In 68 patients (13.2%), at least one episode of decrease in renal function was reported and 31 were transient. Of the 37 patients with permanent progressive renal impairment, eight discontinued treatment. In 48% of the 174 patients reporting any renal event, the event was associated with disease progression [Munshi *et al.* 2011]. The PX-171-003-A1 trial showed that renal function at baseline did not influence treatment outcome [Siegel *et al.* 2012]. The ASPIRE trial included mostly patients with a CrCl of over 50 ml/min. Acute renal failure was reported in 8.4% of KRd patients and 7.2% of Rd patients, confirming the relative safety of carfilzomib on renal function [Stewart *et al.* 2015]. The only exception is the FOCUS trial which showed higher incidence of renal failure events in the Kd group *versus* the Vd group (17.2% *versus* 5%) [Hájek *et al.* 2015]. This might partially be explained by the slightly higher association with disease progression and the higher incidence of baseline (light chain) proteinuria in the carfilzomib group, but the difference in incidence remains large. The overall toxicity profile on renal function of carfilzomib remains relatively safe and dose modifications on the basis of baseline renal function do not seem necessary, however careful monitoring of patients, especially those with (light chain) proteinuria may be prudent. In Figure 2 an overview is givene of adverse events reported in Carfilzomib trials with RRMM.

Carfilzomib and the impact of high-risk cytogenetics

Cytogenetic abnormalities have been a risk-defining factor in the prognosis of MM for a long time [Sawyer, 2011; Jakubowiak *et al.* 2013]. The impact of high-risk cytogenetics [del 13 or hypodiploidy by metaphase cytogenetic analysis or del 17p13, t(4;14), t(14;16) by interphase Fluorescence *in situ* hybridization (FISH)] on single-agent carfilzomib treatment was prospectively analyzed in the PX-171-003-A1 study. Of the 229 patients with available cytogenetics, 62 patients (27.1%) had high-risk cytogenetics *versus* 167 with standard risk. Baseline characteristics were comparable between the two groups, except for a higher number of patients with International Staging System stage III disease and Eastern Cooperative Oncology Group (ECOG) 1/2 performance status. The ORR was comparable between the two groups (24.6% *versus* 25.8%) but DOR (5.6 *versus* 8.3 months) and OS (9.0 *versus* 19.3 months) were shorter in the high-risk group. Analysis of specific cytogenetic anomalies showed that patients with t(4;14) had the highest ORR (38.9%), whereas patients with del 17p13 had the lowest (16.7%). The DOR for both anomalies showed similar differences, with 11.8 months for t(4;14) and 7.0 months for del 17p13. It should be noted though that several patients had at least two abnormalities and were represented in multiple subgroups. ORR, PFS and OS in patients with one anomaly were 30.2%, 3.6 and 10.6 months compared with 15.8%, 2.1 and 8.4 months in the patient group with more than one cytogenetic abnormality. In patients with an isolated t(4;14), the ORR, PFS and OS were 63.6%, 4.5 and 15.8 months respectively [Avet-Loiseau *et al.* 2015]. A subanalysis of the ASPIRE trial showed similar results. Slightly less than a

quarter of patients, both in the KRd and Rd group, had high-risk cytogenetics. The PFS in the KRd group was 2 years, which was 9 months longer than in the Rd group for high-risk patients. ORR was higher in the KRd group (79.2% *versus* 59.6%) with 29.2% of high-risk KRd patients reaching a CR (*versus* 5.8%). DOR (22.2 *versus* 14.9 months) was also significantly higher in the high-risk group. These studies show that carfilzomib can partially overcome high-risk cytogenetics and in combination therapy high and deep response rates can be reached even though these patients still have a worse prognosis than patients without high-risk cytogenetics.

Practical guidelines

The administration time of carfilzomib should be 30 min or more since it has been shown to improve tolerability. In the first administration tumor lysis prophylaxis with hydration is advised and further prophylaxis with rasburicase is prudent in case of a large tumor load. Prophylaxis with allopurinol is not advised due to possible interactions. Dose modifications in patients with baseline renal impairment do not seem necessary. However, renal function should be closely monitored as sudden renal insufficiency has been described. Carfilzomib does not seem to be metabolized by the liver, but has not been tested in patients with severe liver impairment. We advise careful monitoring in patients with liver disease. A good screening method to identify patients at risk of cardiac toxicity is not yet available. Since screening with cardiac ultrasound or NT-proBNP and troponin has not proven useful we advise more intensive clinical monitoring in patients with cardiac comorbidity. All patients should be routinely controlled for fluid overload and development of hypertension. Physicians should be aware of possible development of pulmonary hypertension. Routine evaluations of peripheral blood and platelet counts are mandatory. Herpes zoster prophylaxis is standard of care.

Conclusion

Carfilzomib is a potent proteasome inhibitor with powerful efficacy in heavily pretreated patients with RRMM, including bortezomib and immunomodulatory drugs. The recent ASPIRE trial showed superior response rates and PFS for KRd compared with Rd, even for lenalidomide-refractory patients and a trend in favor of bortezomib and double-refractory patients. Lack of significance in the latter group may be due to the small number of patients. The result from the ENDAEVOR trial also showed superiority of carfilzomib over bortezomib, with a far superior ORR, and PFS, CR and DOR which were all doubled. Furthermore, carfilzomib has the ability to partially overcome the negative impact of high-risk cytogenetics. Carfilzomib seems to be a safe treatment option in specific populations like patients with renal impairment and polyneuropathy, either as a single agent or in combination with immunomodulatory drugs like lenalidomide. A slightly higher incidence of cardiac toxicity is seen, for which further tools for identifying patients at risk are necessary. The different dosing regimens in studies make it difficult to determine an optimal dosing regimen. A more patient-friendly regimen, dosing once a week instead of twice a week, seems to have similar efficacy in newly diagnosed patients with MM [Palumbo *et al.* 2014]. Another important question remains the sequence of treatment schedules. Longer follow up and data on OS from phase III trials will be helpful. Phase I/II studies of carfilzomib in newly diagnosed patients show promising results. Carfilzomib, thalidomide and dexamethasone as induction followed by high-dose melphalan with stem cell transplant, and post-transplant consolidation therapy showed a response rate of 96%, of which 63% had a CR [Sonneveld *et al.* 2015]. The combination of lenalidomide and dexamethasone in Newly Diagnosed Multiple Myeloma (NDMM) showed response rates as high as 98%, of which 61% had a stringent CR in a study in which only 7 out of 53 patients underwent autologous transplant after four cycles and the remainder proceeded with another eight cycles of KRd [Jakubowiak *et al.* 2012]. In a small study in high-risk smoldering myeloma, all 12 patients achieved a CR, including 11 patients (92%) negative for minimal residual disease based on multicolor flow cytometry and next-generation sequencing; 2 of the 12 patients were positive for minimal residual disease in the bone marrow supernatant [Landgren *et al.* 2014]. Phase II/III studies in patients with NDMM are currently underway, after which the role of carfilzomib in first-line treatment will become clearer [Bringhen *et al.* 2014]. New treatment combinations of carfilzomib with new drugs such as the immunomodulator pomalidomide and HDAC inhibitors show promising results for the future.

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