Next-Generation Proteasome Inhibition in Multiple Myeloma

Reports on Carfilzomib from the 53rd Annual Meeting of the American Society of Hematology*

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Advances in the Treatment of Multiple Myeloma: Next-Generation Proteasome Inhibition

by Alice Goodman

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States, with more than 64,000 people living with this disease and about 21,700 new cases diagnosed each year.1 The disease is due to an abnormality in plasma cells that causes them to proliferate in the bone marrow. This can lead to osteolytic lesions and bone destruction in a significant number of patients.2 Over the past decade, the development and implementation of several targeted therapies has revolutionized the treatment of myeloma. These include the first-in-class proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide. In addition to these therapies, numerous investigational agents are now being studied in clinical trials for MM. One such agent is carfilzomib, a next-generation proteasome inhibitor that selectively and irreversibly binds to its target; this results in sustained proteasome inhibition without the off-target effects that occur with bortezomib.3,4

As a single agent, intravenous (IV) carfilzomib has undergone extensive phase 2 evaluation for the treatment of relapsed and/or refractory myeloma (Table). Investigators are also assessing its safety and efficacy when combined with other agents, both in newly diagnosed and pretreated patients. At the 53rd Annual Meeting of the American Society of Hematology (ASH), held December 10-13, 2011, in San Diego, California, poster and oral presentations focused on encouraging results from clinical trials of carfilzomib use in MM.

Single-Agent Carfilzomib

Dose-response relationship in relapsed and/or refractory MM

Squifflet and colleagues presented findings from a pooled analysis of 430 patients from two phase 2 clinical studies in which carfilzomib was given as a single agent for the treatment of relapsed and/or refractory MM.5 A rigorous, multivariate analysis demonstrated a highly significant dose-response relationship with carfilzomib across efficacy end points that included overall response rate (ORR, the primary end point), duration of response (DOR), time to progression, progression-free survival (PFS), and overall survival (OS) (P<.001 for all end points). A dose-response relationship was also observed in the depth of response [PR or better] across the study population. Although a corresponding dose-toxicity analysis has not been completed, thus far, carfilzomib has been shown to have a similar tolerability profile at doses of 20 mg/m² and 27 mg/m².

This analysis was based on nonrandomized trials, and the investigators indicated that it therefore may be subject to bias, some of which can be accounted for by multivariate modeling. Clinical trials are currently under way to evaluate carfilzomib in higher dosing regimens.

Safety of carfilzomib in relapsed and/or refractory MM

Early trials have reported acceptable tolerability with carfilzomib, including low rates of peripheral neuropathy (PN).6 Singhal and colleagues presented updates of a pooled analysis of 526 pretreated patients with relapsed and/or refractory MM who received single-agent carfilzomib in four phase 2 studies (003-A0, 003-A1, 004, 005) to further evaluate the safety of this agent.7

As a single agent, carfilzomib has undergone extensive phase 2 evaluation for the treatment of relapsed and/or refractory myeloma.

Discontinuation of therapy due to toxicities occurred in 15% of patients. Grade 3 and 4 adverse events (AEs) were mostly reversible and primarily hematologic. Neuropathy was generally mild to moderate and did not require dose adjustments. In addition, the rate of this toxicity was low: PN of all grades was reported in 73 patients (14%), with 1 treatment discontinuation (<1%) attributed to PN. Less than 1% of patients discontinued carfilzomib due to renal toxicity, and 87% had stable renal function while on therapy. Cardiac events were reported in 7% of all patients (regardless of causality), but fatal cardiac events possibly related to carfilzomib occurred in less than 2% of the study population. Treatment discontinuations attributed to cardiac events included congestive heart failure (2%), cardiac arrest (1%), and myocardial ischemia (<1%).

The investigators concluded that it was not possible to determine the extent to which these AEs could be attributed to comorbidities present at baseline, toxicity from prior chemotherapies, effects of myeloma, carfilzomib, or a combination of any or all of these factors. However, the rates and causes of death were consistent with those previously reported in pretreated patients with end-stage MM.

Impact of cytogenetics on carfilzomib therapy

Specific genetic abnormalities in patients with MM can result in poor response to therapy and shorter survival.8 According to results of a study reported by Jakubowiak and colleagues, carfilzomib appears to be effective despite the presence of high-risk cytogenetics associated with poor prognosis.9

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Table 1. Phase 2 Clinical Trials of Single-Agent Carfilzomib Use in Multiple Myeloma

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Population</th>
<th>Carfilzomib Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PX-171-003-A0</td>
<td>Phase 2, open-label, single-arm study</td>
<td>Relapsed and/or refractory (N=46)</td>
<td>20 mg/m²</td>
</tr>
<tr>
<td>PX-171-003-A1</td>
<td>Phase 2b, open-label, single-arm study</td>
<td>Heavily pretreated, relapsed and/or refractory, treated with ≥2 prior therapies* (N=66)</td>
<td>20 mg/m² (cycle 1) 20 mg/m² escalated to 27 mg/m² (up to 12 additional cycles)</td>
</tr>
<tr>
<td>PX-171-004</td>
<td>Phase 2, open-label study</td>
<td>Heavily pretreated, relapsed and/or refractory (1-3 prior therapies) (N=164)</td>
<td>Cohort 1: 20 mg/m² (all cycles) Cohort 2: 20 mg/m² (cycle 1) escalated to 27 mg/m² (subsequent cycles)</td>
</tr>
<tr>
<td>PX-171-005</td>
<td>Phase 2, open-label study of safety and pharmacokinetics</td>
<td>Relapsed and/or refractory with renal dysfunction (N=50)</td>
<td>15 mg/m² (cycle 1) 20 mg/m² (cycle 2) 27 mg/m² (cycle 3)</td>
</tr>
<tr>
<td>PX-171-007</td>
<td>Phase 1b/2, open-label study</td>
<td>Relapsed and/or refractory (N=33)</td>
<td>Prolonged infusion with stepped-up dosesa</td>
</tr>
</tbody>
</table>

*aPrior therapies included bortezomib and either thalidomide or lenalidomide. bBortezomib-naive and bortezomib-treated patients. cBortezomib-naive patients. Cycle 1 day 1-2 doses were 20 mg/m², followed by escalation to a higher dose of either 36, 45, 56, or 70 mg/m².

An analysis of the 003-A1 study found that unfavorable cytogenetic characteristics did not adversely impact response to single-agent carfilzomib in heavily pretreated patients with relapsed and/or refractory MM. However, median OS was shorter for those with cytogenetic abnormalities than for those with no detected abnormalities (11.9 months vs 19.2 months). A similar trend was observed for median PFS (3.6 months vs 4.6 months). Of 234 evaluable patients, 75 had ≥1 unfavorable cytogenetic abnormalities including deletion of chromosome 13 (del 13) or hypodiploidy (detected by metaphase cytogenetic analysis) and/or deletion of chromosome 17p13, t(4;14), or t(14;16) (by fluorescence in situ hybridization [FISH]).

The presence of unfavorable cytogenetics did not significantly impact DOR or response rates of patients in this study. ORR was 23% in those with normal cytogenetics versus 30% in those with unfavorable cytogenetics. A trend was observed toward higher response rates in the presence of t(4;14) and lower response rates for t(14;16), but the numbers of patients were too small in these subgroups for statistical significance.

The investigators concluded that the trend toward shorter PFS and OS in the presence of cytogenetic abnormalities in this trial may reflect the lack of effective alternative therapies available after carfilzomib treatment, resulting in a higher discontinuation rate among patients with unfavorable cytogenetics, or the poor prognosis in these patients despite improvement in response with carfilzomib. The role of cytogenetics continues to be evaluated in ongoing clinical trials of carfilzomib.

Rapid response to single-agent carfilzomib

A separate exploratory analysis of two phase 2 studies (003-A1 and 004) by Wang and colleagues showed that rapid responses are achieved with single-agent carfilzomib in patients with relapsed and/or refractory MM. Specifically, they found that minimal response (MR) or better occurs within a median of 0.5 to 1 month.11 This analysis included 257 response-evaluable, heavily pretreated patients from the 003-A1 trial, and 161 response-evaluable patients (bortezomib-naive and bortezomib-treated) from the 004 trial.

When examining the cohorts separately, the investigators found that the heavily pretreated patients in study 003-A1 achieved PR or better at a median of 1.9 months and MR or better at a median of 1 month. In study 004, the bortezomib-naive patients achieved PR or better at a median of 1.7 months and MR or better at a median of 0.5 month and the bortezomib-treated patients achieved PR or better at a median of 1.4 months and MR or better at a median of 1 month.

When results were analyzed according to specific baseline characteristics, a trend was observed toward longer time to clinical benefit rate (MR or better) in patients treated with a greater number of previous therapeutic regimens, although prior autologous stem cell transplant (ASCT) did not appear to affect this rate.

The investigators concluded that the data compare favorably to historical data for agents frequently used in the treatment of relapsed and/or refractory myeloma, including bortezomib, dexamethasone, lenalidomide, liposomal doxorubicin, and thalidomide. In addition, this preliminary analysis represents the first focused evaluation of the dynamics of response to single-agent carfilzomib, and further investigation in the setting of ongoing and future trials is merited.

Safety and efficacy of prolonged carfilzomib infusion

Updated results of the phase 1b/2 007 trial reported by Papadopoulos and colleagues suggest that single-agent carfilzomib can achieve excellent response rates in heavily pretreated patients with relapsed and/or refractory MM.12 The study included 33 patients who progressed on at least 2 prior lines of therapy.
Carfilzomib was administered via 30-minute IV infusions in “stepped up” doses at 4 different levels: 20/36 mg/m², 20/45 mg/m², 20/56 mg/m², and 20/70 mg/m². ORR was 60% with the 20/56-mg/m² dose of carfilzomib (maximum tolerated dose), which the investigators described as “noteworthy” for a heavily pretreated population.

The safety profile for carfilzomib was acceptable. The most common grade 3 or 4 AEs in the 20/56-mg/m² cohort were thrombocytopenia (38%), anemia (21%), hypertension (13%), and pneumonia (13%). The majority of AEs were grade 1 and 2. One patient in the 20/56-mg/m² cohort experienced grade 1 PN.

The investigators concluded that the pharmacokinetic and pharmacodynamic results of this trial reinforce preclinical data showing a dose-response relationship and suggest that longer infusion times allow higher doses of carfilzomib and more robust proteasome inhibition. These findings suggest that higher dosing of carfilzomib may improve efficacy with acceptable safety.

**Carfilzomib use in bortezomib-naive patients**

Vij and colleagues reported final results of study 004, a multicenter, nonrandomized, open-label, phase 2 trial of 164 patients with relapsed and/or refractory MM who were treated with 1 to 3 prior lines of therapy. Cohort 1 consisted of 59 bortezomib-naive patients treated with carfilzomib 20 mg/m² (35 bortezomib-treated patients were also included in cohort 1, but results were reported previously). Cohort 2 included 70 bortezomib-naive patients treated initially with carfilzomib 20 mg/m² (cycle 1), then escalated to 27 mg/m² for all treatment cycles thereafter.

Median age of patients in this study was 65 years, and median time to diagnosis was 3.6 years. Approximately 80% of patients had favorable cytogenetics, and 94% had an Eastern Cooperative Oncology Group performance status of 0-1. Patients received a median of 6 or 7 cycles. Approximately 30% of cohort 1 and 40% of cohort 2 received the full planned cycles of therapy.

Response to carfilzomib treatment (time to achieve PR) was rapid at a median of 1 month for cohort 1 and 1.9 months for cohort 2. Median PFS was 8.1 months for cohort 1 and not yet reached at the time of reporting for cohort 2. ORR (the primary end point of the trial) was 42% in cohort 1 and 52% in cohort 2, and the clinical benefit rate was 59% and 64%, respectively. Median DOR was 13.1 months in cohort 1 and not yet reached in cohort 2.

Toxicities in this trial were mainly hematologic. Notable AEs were fatigue, nausea, anemia, and dyspnea. The rates of grade 3 and 4 toxicity were acceptable. Treatment-emergent PN was reported in 15% of cohort 1 and 19% of cohort 2, but this did not lead to treatment discontinuation. Overall, AEs led to discontinuation in approximately 15% of patients (Table 2).

During an oral presentation at ASH, Dr Ravi Vij, from Washington University School of Medicine, St Louis, Missouri, stated that carfilzomib gains approval for relapsed and/or refractory MM, he envisions that the drug will continue on use in combination regimens and in the frontline setting. “We still don’t know what the best dose of carfilzomib is. Studies have escalated the dose up to 56 mg/m²,” he stated. “Tolerability may be improved by slow infusion, especially at doses above 20 mg/m² (PX-171-007).”

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**Table 2. Number of Cycles Completed and Reasons for Treatment Discontinuation**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No. cycles started</th>
<th>Completed 12 cycles, n (%)</th>
<th>Reason discontinued early, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20 mg/m² (N=59)</td>
<td>70 (1-21)</td>
<td>Progressive disease 24 (40.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adverse events 13 (22.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other 3 (5.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Withdrawn consent 2 (3.4)</td>
</tr>
<tr>
<td>2</td>
<td>20/27 mg/m² (N=70)</td>
<td>6.5 (1-13)</td>
<td>24 (34.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 (10.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 (5.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 (8.6)</td>
</tr>
</tbody>
</table>

*22 patients continued treatment beyond 1 year on the extension protocol 010.

**Multidrug Carfilzomib-Based Therapy**

**Carfilzomib with other agents in relapsed and/or refractory MM**

Usmani and colleagues presented results of a phase 2 study of 81 heavily pretreated patients with relapsed and/or refractory MM who were participating in the UARK Compassionate Use Protocol. Patients in this trial received carfilzomib as a single agent at 20 mg/m² for days 1 and 2 of the first cycle, then the dose was escalated to 27 mg/m² for the rest of that cycle; dexamethasone 4 mg was given with each dose. From cycle 2 onward, patients who failed to achieve PR or better on cycle 1 could receive escalated carfilzomib doses of 36, 45, and 54 mg/m² plus dexamethasone 20 mg. In the absence of PR from cycle 2 onward, additional antimumeloma drugs could be added with subsequent cycles.

Of the 81 patients, 79 had prior ASCT; 60 had at least 2 transplants. All patients had received regimens containing bortezomib, thalidomide, lenalidomide, melphalan, or steroids. During the study, 71 patients discontinued therapy due to progression, death, or toxicity.

At 12 months, OS and PFS rates were 41% and 5%, respectively. In univariate and multivariate analyses, an OS benefit was observed in patients receiving at least 3 cycles of carfilzomib (P<.001). Myelotoxicity (grade 3 or higher) was observed in the majority of patients (anemia, 79%; leukopenia, 83%; and thrombocytopenia, 100%). Grade 1 and 2 PN was present at baseline in 53% of patients; grade 3 or higher PN was seen in 7% of patients after cycle 1 and in 8% after cycle 5. Surprisingly, worsening or new neuropathy was not observed in the majority of patients.

The investigators concluded that combining carfilzomib with other antimumeloma agents on a compassionate-use basis allowed them the opportunity to make observations regarding potential clinical synergy of particular combinations. Specifically, the combination of carfilzomib plus dexamethasone with lenalidomide and vorinostat was shown to be promising in a subset of relapsed and/or refractory MM patients.
Table 3. Best Responses to a Frontline Regimen of Carfilzomib, Lenalidomide, and Dexamethasone.17

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>N</th>
<th>ORR</th>
<th>≥VGPR</th>
<th>sCR/CR/nCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients*</td>
<td>49</td>
<td>46 (94)</td>
<td>32 (65)</td>
<td>26 (53)</td>
</tr>
<tr>
<td>(1 - 20 cycles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>20</td>
<td>18 (90)</td>
<td>13 (65)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>II or III</td>
<td>29</td>
<td>28 (97)</td>
<td>19 (66)</td>
<td>16 (55)</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/favorable</td>
<td>33</td>
<td>30 (91)</td>
<td>20 (61)</td>
<td>17 (52)</td>
</tr>
<tr>
<td>Unfavorable*</td>
<td>16</td>
<td>16 (100)</td>
<td>12 (75)</td>
<td>9 (56)</td>
</tr>
</tbody>
</table>

*Based on 49 patients who completed 1 month of treatment as of cutoff date 6/30/11. *Del 13 by metaphase or hypodiploidy or t(4;14) or t(14;16) or del 17p.
CR indicates complete response; ISS, International Staging System; nCR, near-complete response; ORR, overall response rate; sCR, stringent complete response; VGPR, very good partial response.

Carfilzomib, lenalidomide, and low-dose dexamethasone in newly diagnosed MM

In a phase 1/2 trial by Jakubowiak and colleagues, treatment with a regimen of carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) was shown to be safe and effective for newly diagnosed patients with MM.16 These investigators presented more mature data from their study, which confirmed that CRd was highly active and well tolerated in this population of patients.17

Patients in this trial were placed on 1 of 3 treatment dosing schedules and received 20 mg/m², 27 mg/m², or 36 mg/m² of carfilzomib to determine the maximum tolerated dose. Carfilzomib was administered on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle for 8 cycles. They also received lenalidomide 25 mg on days 1 to 21, and dexamethasone 40 mg weekly for cycles 1 to 4 and 20 mg weekly for cycles 5 to 8.

Transplant-eligible patients who achieved a PR or greater could proceed to stem cell collection (SCC) with growth factor support alone after 4 cycles. There was no difficulty in harvesting stem cells from patients treated with CRd; 100% of attempted stem cell harvests were successful in the 24 patients in whom harvest was attempted.

There was no difficulty in harvesting stem cells from patients treated with CRd; 100% of attempted stem cell harvests were successful in the 24 patients in whom harvest was attempted.

All patients received 4 more cycles of CRd, with transplant-eligible patients having the option to proceed with ASCT. Patients who continued therapy beyond 8 cycles received maintenance CRd (carfilzomib on days 1, 2, 15, 16; lenalidomide on days 1-21; and dexamethasone weekly) in 28-day cycles at the doses tolerated at the end of 8 cycles.

Median age of patients was 59 years; 43% were aged 65 years or older. One third had unfavorable cytogenetics: del 13 (by metaphase) or hypodiploidy or t(4;14) or t(14;16) or del 17p (by FISH).

Responses to CRd were rapid. Of the 49 response-evaluable patients, 46 achieved PR or better after 1 cycle with 100% achieving PR or better after 4 cycles, 100% achieving very good partial response (VGPR) or better after 12 cycles, and 79% achieving complete response (CR)/near-CR after 12 cycles. Responses to CRd were also durable and were not affected by stage or cytogenetics (Table 3). At 9.5 months of follow-up, only 1 patient had progressed and all patients were still alive.

The CRd regimen was also well tolerated. Grade 3/4 thrombocytopenia was reported in ~10% of patients, anemia in ~18%, and neutropenia in ~12%. No grade 3/4 PN was reported.

The investigators concluded that the responses seen with CRd compared favorably to the best frontline regimens currently used for MM. This combination provided rapid response, and DOR increased with longer duration of treatment. Toxicities were manageable and there was a limited need for dose modification.

Carfilzomib, thalidomide, and dexamethasone as induction prior to high-dose melphalan in newly diagnosed MM

A phase 2 trial from the Erasmus Medical Center and the European Myeloma Network evaluated an induction regimen of carfilzomib, thalidomide, and dexamethasone (CARTHADEX) in patients with newly diagnosed MM who were candidates for high-dose therapy.18

Sonneveld and colleagues reported on 45 patients enrolled in this trial who were evaluable for response and safety. Patients received induction therapy with 4 cycles of carfilzomib at 20/27 mg/m², plus thalidomide 200 mg, and dexamethasone 40 mg on a 28-day cycle. SCC was performed with cyclophosphamide 2 g/m² and growth factor support. After high-dose melphalan (200 mg/m²) and ASCT, consolidation therapy was given with 4 cycles of carfilzomib 27 mg/m², thalidomide 50 mg, and dexamethasone 40 mg.

SCC was successful in 100% of patients (N=16) at the time of the report. Four patients discontinued therapy: 2 who developed progressive disease and 2 who experienced severe AEs in cycle 1. After induction therapy, the ORR was 84% (CR, 16%; VGPR, 29%; PR, 39%).

Grade 1 and 2 PN was reported in 24% of patients, mostly related to thalidomide; 4% had grade 3 tumor lysis syndrome. Grade 1 and 2 gastrointestinal toxicity was observed in 4% of patients, and grade 3 in 4%. Grade 1 and 2 infection was reported in 4%, and grade 3 in 4%.

During an oral presentation, Dr Pieter Sonneveld, from Erasmus
Medical Center, Rotterdam, stated, “Thus far, bortezomib has been the most effective regimen prior to high-dose therapy in transplant-eligible patients with MM. Bortezomib, thalidomide, and dexamethasone (VTD) produces the highest CR rate after induction and after high-dose melphalan and ASCT. VTD is also effective consolidation therapy, which further improves response. CARThADEX builds on VTD, replacing bortezomib with carfilzomib. Our study showed that this induction regimen is feasible and tolerable. The response after induction is rapid and equals that seen with VTD.”

Conclusion and Future Directions

There has been remarkable progress in the treatment of MM over the past several years, and it is clear that the use of newer, targeted therapies has contributed substantially to this reality. The next generation of antimyeloma agents offers the promise of improving outcomes even further. As shown in recent phase 2 studies, carfilzomib is safe and effective as a single agent and in combination regimens. In particular, it produces less PN than bortezomib, and other toxicities appear manageable.

Carfilzomib is now being studied in two phase 3 trials. The ASPIRE (CArfilzomib, Lenalidomide, and Dexamethasone versus Lenalidomide and Dexamethasone for the treatment of Patients with Relapsed Multiple Myeloma, PX-171-099) trial is an international, randomized phase 3 trial that is evaluating the safety and efficacy of the combination of lenalidomide and low-dose dexamethasone, with and without carfilzomib, in patients with MM treated with 1 or more prior therapies. The FOCUS (CarFilOmib for AdvanCed Refractory MUltiple Myeloma European Study, PX-171-011) trial is evaluating single-agent carfilzomib in patients with relapsed and/or refractory MM who have received 3 or more prior therapies versus best supportive care.

References


Green Hill Healthcare Communications
The Emerging Role of Carfilzomib in Multiple Myeloma

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Introduction

The proteasome inhibitor carfilzomib is a promising new agent for the treatment of multiple myeloma (MM). Data presented at the 53rd Annual Meeting of the American Society of Hematology (ASH) highlighted a role for this agent in both the frontline and relapsed and/or refractory settings.

Carfilzomib irreversibly binds to and inhibits the chymotrypsin-like activity of the 20S proteasome. This agent differs both structurally and mechanistically from bortezomib, exhibiting sustained and more intense proteasome inhibition. Consequently, carfilzomib is proving to be an important new drug in MM, with presentations at ASH helping to elucidate the optimal place of this agent in therapy.

Recent Data on the Safety and Efficacy of Carfilzomib

In addition to evidence suggesting improved clinical outcomes, it appears that carfilzomib is better tolerated than bortezomib. Data from multiple studies indicate low rates of peripheral neuropathy, allowing for the use of this agent over an extended number of cycles without the need for dose reduction. Overall, the most frequently reported adverse events (AEs) associated with carfilzomib use include fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia. The most common grade 3 or higher toxicities are thrombocytopenia, anemia, lymphopenia, pneumonia, and neutropenia. Most of these AEs are reversible and usually do not require discontinuation of therapy.

According to updated results from a phase 1b/2 study, single-agent carfilzomib can be used at a dose as high as 56 mg/m² when administered as a 30-minute infusion in a “stepped-up” regimen, in which patients begin with a lower dose (20 mg/m²) for the first 2 cycles of therapy. This strategy resulted in increased pharmacodynamic response and acceptable tolerability in a heavily pretreated population of patients with relapsed and/or refractory disease. Ongoing trials are evaluating whether increased proteasome inhibition will result in improved clinical outcomes among patients with MM.

In separate clinical trials, treatment with single-agent carfilzomib also showed promising activity in the relapsed and/or refractory setting in patients who were bortezomib-naive or who had unfavorable cytogenetic abnormalities. These studies confirm previous phase 1 investigations and establish a dose-response relationship across several relevant end points. The parallel analysis of dose-toxicity relationship is still outstanding in some studies, and these results will be important, as the optimal dose and infusion method have not yet been identified.

Findings from trials using multidrug regimens, both in newly diagnosed and relapsed and/or refractory myeloma, were also presented at ASH. These are some of the most exciting results, as they indicate the potential clinical synergy of carfilzomib with other agents, particularly immunomodulators. In the case of patients with newly diagnosed MM who are candidates for high-dose melphalan and autologous stem cell transplant, a regimen of carfilzomib, thalidomide, and dexamethasone appears to show similar outcomes to bortezomib-based therapy. In addition, newly diagnosed patients (transplant and nontransplant candidates) who received a combination of carfilzomib, lenalidomide, and dexamethasone tolerated treatment well, and achieved rapid and deep responses. As in the single-agent studies, these results paint a promising picture for frontline treatment, both from tolerability and efficacy perspectives, while still leaving unresolved issues such as optimal dose, infusion time, and potential drug combinations.

Conclusion

Taken as a whole, recent data on carfilzomib use offer an exciting perspective on what promises to be an important new player in the treatment of a challenging disease. Although some questions remain unanswered and others have emerged, it is clear that given the level of clinical responses and favorable tolerability, carfilzomib stands poised to assume a prominent role in the treatment of patients with MM.

References


NURSE PERSPECTIVE

Carfilzomib: A New Agent in the Treatment Armamentarium for Multiple Myeloma

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Introduction

A 1998 study by the Myeloma Trialists’ Collaborative Group compared conventional chemotherapy (CCT) with melphalan plus prednisone (MP)—the previous standard of care for the treatment of patients with multiple myeloma (MM).1 This analysis included 6633 patients from 27 randomized trials. Researchers found no difference in mortality between treatment with CCT and treatment with MP.2 Since this analysis was reported nearly 14 years ago, the landscape of MM has changed dramatically—and for the better.

It has been well described by many authors that median overall survival (OS) rates among patients with MM are on the rise.3 This is due, in part, to improved treatment and supportive care, as well as an enhanced understanding of the biology of the disease. Insight into the ways in which myeloma cells thrive has given researchers the ability to develop novel, targeted agents that are now regarded as the new standard of care for the treatment of MM. These include the first-generation immunomodulatory drug, thalidomide, its analog, lenalidomide, and the first-in-class proteasome inhibitor, bortezomib.

Novel Targeted Agents for Multiple Myeloma

The antitumor activity of thalidomide in patients with relapsed and/or refractory MM was first reported by Singhal and colleagues in 1999.4 When individuals who had been previously treated with high-dose chemotherapy received this drug, 8 of the 84 patients treated experienced a ≥90% reduction in serum or urine levels of paraprotein.5 In 2006, the US Food and Drug Administration (FDA) granted approval for thalidomide in combination with dexamethasone for newly diagnosed MM patients.6 Over the past several years, thalidomide has become an important drug in the treatment armamentarium for myeloma, and is used in both the frontline and relapsed and/or refractory settings.

Bortezomib was the next targeted agent to demonstrate efficacy in myeloma. The international, randomized, phase 3 APEX trial led to the approval of bortezomib in 2005 for the treatment of patients with MM who had received at least 1 prior therapy.7 Patients who received bortezomib in this study had a significantly longer median time to progression (TTP) than those who received dexamethasone (6.2 vs 3.5 months, respectively; P<.001), as well as higher response rates (38% vs 18%, respectively; P<.001) and improved survival (1-year survival rate: 80% vs 66%, respectively; P=.003).8 Subsequently, bortezomib has also received FDA approval as an initial treatment for patients with MM, based on results of the pivotal phase 3 VISTA trial.9

Dimopoulos and colleagues published results of studies assessing OS among heavily pretreated patients with relapsed and/or refractory MM who received lenalidomide plus dexamethasone or dexamethasone plus placebo.7 The MM-009 and MM-010 studies were 2 large, placebo-controlled, randomized, phase 3 trials that included more than 704 patients. Individuals treated with lenalidomide plus dexamethasone exhibited a significantly improved median TTP compared with those who were treated with dexamethasone alone (13.4 vs 4.6 months, respectively;
In addition, lenalidomide plus dexamethasone versus dexamethasone plus placebo significantly improved overall response rates (60.6% vs 21.9%, respectively; P<.001) and complete response rates (15.0% vs 2.0%, respectively; P<.001). Since 2006, lenalidomide has been FDA-approved for use in combination with dexamethasone for patients with MM who have received at least 1 prior therapy. 

Carfilzomib, a next-generation proteasome inhibitor, is showing encouraging efficacy as single-agent treatment in patients with relapsed and/or refractory MM. The activity of this agent also appears to be enhanced when it is combined with antimyeloma drugs such as lenalidomide and dexamethasone. The safety profile of carfilzomib is impressive, especially the low rates of neuropathy reported in recent trials (Figure). Peripheral neuropathy (PN) is a challenging adverse event associated with several novel therapies for MM, and it can be especially problematic in the relapsed and/or refractory setting. From a nurse’s perspective, the ability to offer patients therapy that will not significantly increase the risk of PN is especially appealing, as it allows better quality of life and increases the possibility that they will remain on treatment.

Conclusion

Over the past 12 years, I have had the opportunity to participate in the care of numerous patients with MM and have acquired first-hand knowledge of the benefits of novel agents. Through the context of clinical trials, many established and investigational agents have been evaluated for the disease. It is gratifying to know that an agent such as carfilzomib may soon be available for patients whose myeloma continues to progress despite prior therapy. We continue to welcome research and encourage clinical trial participation to develop additional therapeutic strategies that will benefit patients in the future.

References

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