“New drugs in multiple myeloma – role of carfilzomibe and pomalidomide

Typ artykułu:
Praca poglądowa

Tytuł angielski:
“New drugs in multiple myeloma – role of carfilzomibe and pomalidomide”

Streszczenie:
Carfilzomib (CFZ)- an epoxyketone with specific chymotrypsine-like activity is a second-generation proteasome inhibitor with a significant activity in patients with relapsed and refractory multiple myeloma (MM). On July 20, 2012, the US Food and Drug Administration approved CFZ to treat patients with multiple myeloma who have received at least two prior therapies including bortezomib (BORT) and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Pomalidomide (POM) is a novel immunomodulatory derivative (IMID) with stronger in vitro anti-myeloma effect if compared with “older” IMIDs- thalidomide and lenalidomide (LEN). On February 8, 2013, the US Food and Drug Administration approved POM for the treatment of MM patients who have received at least two prior therapies including LEN and BORT and have demonstrated progression on or within 60 days of completion of the last therapy.

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New drugs in multiple myeloma – role of carfilzomibe and pomalidomide.

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Carfilzomib (CFZ) an epoxyketone with specific chymotrypsine-like activity is a second-generation proteasome inhibitor with significant activity in patients with relapsed and refractory multiple myeloma. On July 20, 2012, the US Food and Drug Administration approved CFZ to treat patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Cytogenetic abnormalities did not appear to have an significant impact on the CFZ activity. CFZ was well tolerated and demonstrated promising efficacy in patient with renal insufficiency. Pomalidomide (CC-4047) is a novel immunomodulatory derivative (IMID) with stronger in vitro anti-myeloma effect if compared with “older” IMIDs- thalidomide and lenalidomide. On February 8, 2013, the US Food and Drug Administration approved POM (Pomalyst, Celgene) for the treatment of MM patients who have received at least two prior therapies including LEN and BORT and have demonstrated progression on or within 60 days of completion of the last therapy. POM is a novel IMIDs with a significant anti-myeloma activity and manageable toxicity. This compound has shown the high efficacy in MM
patients who were resistant to prior use of LEN/BORT as well as in the patients with high-risk cytogenetic profile. CFZ and POM has very high efficacy and it will be used also in first line therapy in future.

Carfilzomib (CFZ), an epoxyketone with specific chymotrypsine-like activity is a second-generation proteasome inhibitor with significant activity in patients with relapsed and refractory multiple myeloma [1]. CFZ selectively inhibits a chymotrypsin-like (β5) subunit activity of the 20S proteasome and has minimal cross-reactivity with other protease classes. This inhibition is irreversible, dose- and time-dependent in vitro and in vivo. As a result of proteasome inhibition we observe the accumulation of polyubiquitinated proteins and induction of apoptosis in many tumor cell lines including not only the multiple myeloma but also Waldenström macroglobulinemia, acute myeloid leukaemia, B-cell malignancies (Burkitt’s and NHL), pancreatic cancer, lung carcinoma [2,3].

The efficacy of CFZ in heavily pretreated, relapsed and refractory multiple myeloma has been evaluated in a number of phase II trials. The
pivotal PX-171-003-A1 study of single-agent CFZ enrolled 266 patients [1].

The median age was 63 years and the patients had received a median of 5 prior therapies including lenalidomide, bortezomib, thalidomide, alkylating agents, steroids, antracyclines and transplants. CFZ was administered intravenously (for 3 weeks in each of 4 weeks cycle), twice weekly, at a daily dose of 20 mg/m$^2$ in cycle 1 and then at a dose of 27 mg/m$^2$ twice weekly for up to 12 cycles. The ORR was 23.7%, the clinical benefit response (CBR) was 37%, the median PFS was 3.7 months and the median duration of response (DOR) was 7.8 months. [CBR = ORR (sCR+CR+VGPR+PR) + MR (minimal response)]. The median OS in group of patients refractory to both bortezomib and lenalidomide was 11.9 months. Cytogenetic abnormalities did not appear to have a significant impact on the CFZ activity. The ORR in patients with unfavourable cytogenetic or FISH was higher (29.6%) compared with patients with normal-favourable cytogenetics/FISH (22.8%) although the newest data revealed similar ORR in both groups but significant higher OR in standard risk group [32].

The study PX-171-004 with single-agent CFZ evaluated two groups of patients: first bortezomibe-naive and second previously treated with bortezomibe. In the bortezomibe-naive cohort the ORR was 47.6% and CBR was 61.9% after six cycles of therapy[4]. In the bortezomibe-treated cohort an ORR was 17.1% and CBR was 31.4%. The median DOR was > 10.6 months, while the median TTP and median PFS were 5.3 months [5].

The patients with renal insufficiency were evaluated in PX-171-005 study. CFZ was administered at a dose of 15 mg/m$^2$ in cycle 1, then was escalated to 20 mg/m$^2$ in cycle 2 and to 27 mg/m$^2$ from cycle 3 up to 12 cycles.
[6]. The similar assessment was summarized in Badros AZ study [7]. The pharmacokinetics and safety of carfilzomib were not influenced by the degree of baseline renal impairment, including in patients on dialysis, and carfilzomib was well tolerated and demonstrated promising efficacy [6][7].

CFZ has an acceptable tolerability profile. The incidence of grade 3 and 4 adverse events is low [8]. In the pivotal PX-171-003-A1 trial a grade 3 or 4 thrombocytopenia and anemia were observed in 29 and 24% of patients respectively. They were not dose limiting and did not result in treatment discontinuation. In PX-171-005 study the incidence of adverse events was independent of renal status [6].

Recommended dosage of intravenous CFZ in relapsed, or relapsed and refractory, multiple myeloma is 20 mg/m² on days 1, 2, 8, 9 15 and 16 of the 28-day treatment cycle. If the therapy is well tolerated in cycle 1, the dose should be increased to 27 mg/m² in subsequent cycles. The maximum BSA to be used for dose calculation is 2.2 m². Therapy with CFZ should be continued until disease progression or unacceptable toxicity occurs [9].

On July 20, 2012, the US Food and Drug Administration approved CFZ to treat patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Several trials of CFZ were presented at the 2012 ASH meeting. There were combination of CFZ with thalidomide and dexamethazone reported by Sonneveld P [10] and thalidomide, dexamethazone and cyclophosphamide

All these drugs combinations have shown its effectiveness in resistant, refractory MM patients. The results are encouraging, and need the confirmation on larger cohorts of patients.

In conclusion CFZ is a second-generation proteasome inhibitor with substantial activity in heavily pretreated multiple myeloma patients. CFZ is well tolerated with low number of patients discontinuing therapy due to adverse events. No peripheral neuropathy was connected with CFZ, even in patients with baseline symptoms. CFZ was well tolerated and demonstrated promising efficacy in patient with renal insufficiency.

We are also waiting for results of ongoing trials assessing CFZ [*ENDEAVOR Study*: A Randomized, Open-Label, Phase 3 Study of Carfilzomib Plus Dexamethasone vs. Bortezomib Plus Dexamethasone in Patients with Relapsed Multiple Myeloma, *FOCUS Study*: A randomised, Open-label, Phase 3 Study of Carfilzomib vs Best Supportive Care in Subjects with Relapsed and Refractory Multiple Myeloma, *ASPIRE Study*: A randomised, Multicenter, Phase 3 Study Comparing Carfilzomib. Lenalidomide, and dexamethasone (Crd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Relapsed Multiple Myeloma], which may supply us with a fresh look on CFZ in multiple myeloma.
Another new drug in therapy of multiple myeloma is Pomalidomide (CC-4047) - novel immunomodulatory derivative (IMID) with stronger \textit{in vitro} anti-myeloma effect if compared with “older” IMIDs- thalidomide and lenalidomide. IMIDs are found to be highly effective in myeloma patients and their anti-cancer activity includes several mechanisms. Namely, they may induce apoptosis via caspase-8, inhibit angiogenesis and cytokine secretion and impede the interactions between stroma and myeloma cells [15]. Finally, the protein cereblon (CRBN) has been recently identified as a target for IMIDs. Low CRBN expression was found to be associated with IMID resistance in myeloma cell lines. It was demonstrated that CRBN targets the interferon regulatory factor 4 which plays a crucial role in myeloma cell survival. Moreover it down-regulates tumor necrosis factor-\(\alpha\) [16]. It has also been observed that a decreased CRBN mRNA expression correlated with shorter progression-free survival and overall survival in patients with refractory and relapsed multiple myeloma (MM) [17].

The efficacy, safety and immunomodulatory effects of pomalidomide (POM) as a single agent in relapsed/refractory MM have been explored in two phase I studies. A total of 24 MM patients were included in the study of Schey \textit{et al}. [18]. The maximum tolerated dose was established to be 2 mg daily. Nineteen out of the 24 patients continued study beyond four weeks. It was demonstrated that despite a median of three prior lines of therapy including thalidomide and autologous hematopoietic stem cell transplantation (AHSCT), 67\% of the patients achieved at least 25\% reduction in monoclonal protein concentration, 54\% experienced a greater than 50\% decrease and in 4 out of the 24 patients (17\%) the criteria for complete response (CR) were met. Moreover, \textit{in vivo} T-cell costimulation of this compound was also noted. Namely,
it significantly increased serum interleukin (IL)-2 receptor and IL-12 levels. It should be emphasized that POM was well tolerated and no serious non-hematologic adverse events were observed. However, regarding the safety concerns, there was a single report demonstrating the higher risk of deep vein thrombosis in MM patients on POM [19]. The same group reported on the results of phase I study with alternate day POM. They included 20 heavy pretreated patients and 50% of them achieved greater than 50% decrease in paraprotein. 10% of included patients met criteria for CR. The authors concluded that alternate day POM retained strong anti-myeloma activity whilst decreasing the incidence of thromboembolism [20]. However, it should be noted that these studies were performed in a pre-bortezomib and pre-lenalidomide era. Recently, the results of phase I study of POM in MM patients treated previously with bortezomib (BORT) and lenalidomide (LEN) have been published. Oral POM was administered on days 1-21 of each 28-day cycle. Thirty-eight patients who had received median of 6 prior therapies with BORT and LEN were included in this study. Dexamethasone (DEX) at 40 mg daily was allowed from the 4th cycle for those who progressed or had achieved less than minimal response. The maximum tolerated dose of POM was established to be 4 mg for 28-day cycle. Finally, DEX was added to POM in 22 patients. 21% of the patients achieved >50% decrease of paraprotein and 3% fulfilled the CR criteria. The toxicity was manageable [21].

The first phase II study of POM in combination with low-dose DEX (POM/DEX) in relapsed MM enrolled sixty patients. POM was administered orally at 2 mg daily on days 1-21 of a 28-day cycle whereas DEX 40 mg daily weekly. 63% of evaluated patients responded. Twenty patients (33%) achieved greater than very good partial response (VGPR), including 3 who met criteria for CR. The efficacy of this
combination was also seen in patients with prior refractory to thalidomide (37%), LEN (40%) and BORT (60%) treatment. Moreover, 74% of the patients with high-risk cytogenetic profile responded to the therapy. Myelosuppression was the most common toxicity [22]. The Mayo Group reported the results of POM/DEX combination in MM patients refractory to LEN. Thirty-four patients were included in this study and overall response rate (ORR) was 47% including 11 cases with at least partial response (PR). The median overall survival (OS) was 13.9 months [23]. The same group compared the efficacy of two different doses of POM (2 mg and 4 mg) in the patients with dual refractoriness to LEN and BORT. DEX at 40 mg was administered weekly. A total of 70 patients (35 in each cohort) was enrolled. Any response to treatment in 2-mg group was demonstrated in 49% of patients whereas ORR was 43% for 4-mg cohort. It should be emphasized that responses in both cohorts were rapid and durable, however the follow-up was too short to draw final conclusions. OS at 6 months was estimated to be 78% and 67% for 2mg and 4mg groups respectively. Nevertheless, the results of this trial were highly encouraging if we consider the studied population and that there was no dose-response effect. However, one should keep in mind the frequent occurrence of severe myelosuppression, especially neutropenia and thrombocytopenia observed in this study. It may be partially explained by refractoriness of disease and prior treatment. The risk of thrombotic complications remained low while on low-dose of DEX and adequate prophylaxis. 11% of the patients had peripheral neuropathy of grade 2 in both dose cohorts [24]. The follow-up results of the above-mentioned study based on 345 MM patients were presented during the ASH Meeting in 2012. At least PR was seen in 34% of the patients [25]. Recently, the results of two different dose regimens of POM/DEX in LEN and BORT refractory MM have been presented by French
Myeloma Group. Eighty-four patients with a median of 5 prior lines of therapy were included in this randomized study. POM at 4mg daily was administered continuously for 28 days over 28-day cycle or for 21 days of 28-day cycle. ORR was similar between groups: 34% and 35% respectively. After the median follow-up of 23 months, the median survival was 14.9 months with 44% of patients alive [26]. Finally, the up-to-date largest multicenter randomized phase III study comparing POM/DEX versus high-dose DEX alone was recently initiated. 455 patients with dual refractoriness (LEN and BORT or intolerant to BORT only) were enrolled in this study. Progression-free survival was significantly longer in POM/DEX group if compared with DEX alone (15.7 weeks vs 8.0 weeks), the benefit regarding overall survival was also noted for this former subgroup (median not reached vs 34 weeks) [27].

The combinations of POM with other agents were also tested in the patients with refractory and relapsed MM. Palumbo et al. presented the results of phase I/II study of POM combined with cyclophosphamide and prednisone (PCP) in LEN refractory/relapsed patients. At least PR was documented in 73% of the patients resistant to LEN [28]. An overall response rate of 60% (including 27% meeting the criteria for very good partial response) in refractory MM patients was achieved in combination of POM/DEX and clarithromycin [29].

The toxicity of POM/DEX combinations in heavily pretreated MM patients is acceptable. Neutropenia grade ¾ remained the major hematologic toxicity [25]. Among non-hematologic adverse events, fatigue was the most common complaint [24]. The frequency of thrombotic complications was low and occurred in about 3% of the patients [25]. A small proportion of patients may suffer from peripheral neuropathy [24] or noninfectious pulmonary injury [30].
On February 8, 2013, the US Food and Drug Administration approved POM (Pomalyst, Celgene) for the treatment of MM patients who have received at least two prior therapies including LEN and BORT and have demonstrated progression on or within 60 days of completion of the last therapy. This approval was based on the results of phase II study with a total of 221 patients resistant to LEN/BORT. Patients were randomized to receive 4mg daily POM alone for 21 days of 28-day cycle vs POM/DEX. At least PR was achieved in 15% and 34% of patients respectively [31].

In conclusion, POM is a novel IMIDs with a significant anti-myeloma activity and manageable toxicity. This compound has shown the high efficacy in MM patients who were resistant to prior use of LEN/BORT as well as in the patients with high-risk cytogenetic profile.

Finally, although this article focuses primarily on these agents in the relapse setting, it should be noted that once evaluated in the relapse setting, these agents will ultimately be evaluated in newly diagnosed patients. Thus is the case with an ongoing Phase 3 clinical trial of elotuzumab plus lenalidomide and dexamethasone, compared to lenalidomide and dexamethasone alone, in the frontline treatment of myeloma. Also, once approved, many of these agents have increased efficacy when combined with different class drugs. For example, CRF, lenalidomide and dexamethasone is a very potent regimen for relapse and frontline therapy.

In summary, the future pipeline for myeloma agents is very promising. Although myeloma is only 1 percent of all cancers, six of the 21 agents approved over the past 12 years to treat cancer have been for myeloma, and more myeloma agents appear on the horizon. Soon, we truly will be able to state with confidence that myeloma is a chronic disease with multiple treatment options that can control the disease for years.
REFERENCES:


single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib. Br J Hematol; 2012; 158, 739-748.


10. Sonneveld P, Asselbergs E, Zweegman S, et al. Carfilzomib combined with thalidomide and dexamethasone (CTD) is a highly effective induction and consolidation treatment in newly diagnosed patients with multiple myeloma (mm) who are transplant candidates. Paper presented at: 54th American


dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide 

dexamethasone in myeloma refractory to both bortezomib and lenalidomde: 
comparison of 2 dosing strategies In dual-refractory disease. Blood 2011; 118: 
2970-2975.

25. Lacy MQ, Kumar SK, LaPlant BR, et al. Pomalidomide plus low-dose 
dexamethasone (Pom/Dex) in relapsed myeloma: long term follow up and 
factors predicting outcome in 345 patients. Blood (American Society of 
Hematology Annual Meeting) 2012; 120: abstract 201.

is active and well tolerated in bortezomib and lenalidomide-refractory multiple 

low-dose dexamethasone: demonstrates a significant progression free 
survival and overall survival advantage, in relapsed/refractory MM: a phase 3, 
multicenter, randomized, open-label study. Blood (American Society of 

cyclophosphamide-prednisone (PCP) in patients with multiple myeloma 
relapsed/refractory to lenalidomide. Blood (American Society of Hematology 
Annual Meeting) 2012; 120: abstract 446.


Wykaz plików

Treść artykułu

Treść 1 - Pobierz plik źródłowy (63.5 kB)