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Impact of Cumulative Dose of Carfilzomib in Combination with Lenalidomide and Desamethasone in Relapsed Refractory Myeloma Patients: A Retrospective Real Life Survey of the Sicilian Myeloma Network

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Abstract

Background: Triplet-based lenalidomide plus dexamethasone (Rd) combinations have become the new standard of care for early relapse and refractory multiple myeloma (RRMM). Carfilzomib is a novel selective proteasome inhibitor (PI) with high efficacy in RRMM. The ASPIRE phase 3 trial showed the superiority of carfilzomib-based triplet (KRd compared to Rd), leading to approval of K for RRMM. However, little is known about safety and efficacy of KRd outside a clinical trial context.

Experimental design and aims: In 11 Sicilian Centers belonging to the Sicilian Myeloma Network, from November 2016, when KRd regimen was approved in Italy, to June 2018, 103 consecutive RRMM patients (previous lines 1-10) have received KRd regimen, according to ASPIRE schedule. Lenalidomide dosage was reduced in patients with a low count of platelet and/or renal failure according to manufacturer guidelines.

Since previous studies have demonstrated that increased cumulative dose of first generation PI bortezomib significantly improved overall survival of patients treated with VMP regimen, we studied the effect of cumulative dose of Carfilzomib in RRMM patients receiving KRd.

Results: Clinical and demographic characteristics of patients included in the study are summarized in Table 1.

Median age was 65 years (range 33-86), most patients were males (54%). About half of the patients included in the survey were refractory to previous treatment (54%); Sixty-five (63%) patients received at least 5 cycles of KRd and 38 (36%) received at least 10 cycles.

Overall response rate was 34% (35 patients); 18 patients (17%) achieved a complete response (CR), 6 patients minimal response (MR), 13 (12%) patients achieved PR, 16 patients achieved MR and then progressed; progression occurred in 20 patients, among them 3 did not reached any response.

Delays due to adverse events were 33%, mainly due to febrile neutropenia (22%), thromboembolic events (4.5%), heart failure (3%), or thrombocytopenia (4.5%). To prevent hematological toxicities, 24% of patients received granulocyte growth factors, 15% erythropoietin.

In 30 patients treatment was reduced (mainly due to lenalidomide toxicity) and in 5 patients discontinued for toxicity. Thus, median cumulative carfizomib doses at 2, 3, 4 and 6 cycles were respectively 480 mg (282 mg/m2), 735 mg (435 mg/m2), 995 mg (589 mg/m2) and 1522mg (890 mg/m2).

After a median follow up of 16.2 months, PFS at 12 months was 67.3%. We found that median PFS was significantly longer in patients who received at least 480 mg (282 mg/m2) within first two months of treatment compared to those that could not receive full-dose KRd (respectively, undefined vs 11 months p=0.04).

To identify patients that could obtain the most advantage by KRd treatment, 65 patients who had received at least six cycles were distinguished in two groups, based on previous treatments. In group A, 27 patients were heavily pretreated (median previous lines 4, range 2-10) and had previously received lenalidomide while 38 patients included in group B were less pretreated (median previous lines 3, range 1-5) and lenalidomide- naïve. We found that group A had lower PFS than group B although duration of PFS from the previous treatment was similar in both groups.

Conclusions: In our cohort of patients rate of VGPR or better obtained with KRd combination was high with an overall response rate of 34%, with an acceptable safety profile. It is therefore reasonable that approaches to achieve a higher cumulative dose, such as continuing therapy in responding patients and/or proactive adverse events management, influence efficacy. In addition, it is likely that patients not previously exposed to several lines of treatment including lenalidomide are the best candidate for a favorable outcome with KRd regimen.

graphic

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Disclosures

Di Raimondo:*Celgene:* Honoraria; *Takeda:* Honoraria, Research Funding.

Topics: carfilzomib, dexamethasone, lenalidomide, multiple myeloma, toxic effect, adverse event, bortezomib, complete remission, erythropoietin, febrile neutropenia

Author notes

* Asterisk with author names denotes non-ASH members.

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