Advantages and Drawbacks of Carfilzomib *vs*. Bortezomib

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In myeloma therapy, various biological parameters are considered to have an effect on disease evolution and guiding the course of treatment. In the present study we have enrolled 105 patients with Multiple Myeloma admitted in the Hematology Department within the City Emergency Clinical Hospital Timisoara over a 4-year period. This study aims to assess the adverse events, response and overall survival after administration of bortezomib and dexamethasone vs. carfilzomib and dexamethasone regimens.

Keywords: Carfilzomib, Bortezomib, Multiple myeloma

Multiple myeloma (MM) is a neoplasia with heterogeneous plasma cells exhibiting a large range of clinical signs and symptoms [1]. Although highly effective therapies are available, survival varies greatly, ranging from a few months to a few years.

"Myeloma Therapy" in guidelines includes a list of primary therapeutic regimens recommended for the transplant candidates and for the non-transplant group of patients, as well as a list of recommended agents for maintenance therapy. The list does not include all the regimens.

Multiple myeloma treatment commonly involves the use of sequential regimens to achieve prolonged remission with acceptable toxicity. The introduction of new agents, particularly immunomodulatory derivatives (IMiDs), thalidomide and lenalidomide, as well as the proteasome inhibitor, bortezomib, increased the achievement and durability of remission, leading to improved survival in this malignancy [1]. However, resistance to these agents was recorded at some point. "Double-refractory" is a term used for those patients who are resistant and/or intolerant to both lenalidomide and bortezomib, and who have poor prognosis. Identification of new effective agents to treat double-refractory myeloma is a high priority [1].

Siegel *et al.* reported the results of a large phase II clinical trial of the new proteasome inhibitor carfilzomib in patients with progressive disease who received all classes of effective agents, including bortezomib [2]. Carfilzomib differs from bortezomib, the proteasome inhibitor prototype, in that it irreversibly and more selectively binds to proteasome, primarily by inhibiting the chymotrypsin-like activity of this enzyme [2, 3]. Patients in these studies were previously exposed to five treatment regimens on average, with 28% knowing to have adverse cytogenetic abnormalities, whereas 80% were considered double-refractory [2-4]. In case of single-agent carfilzomib, the overall response rate was 23.7%, while double-refractory patients had 20.1% response rate. Although progression-free survival was rather short (3.7 months), the response duration for patients achieving at least partial remission was encouraging (7.8 months) and comparable over all subgroups, including the double-refractory ones [5]. Median survival in the whole group was also promising, of 15.6 months; those with double-refractory myeloma had an overall survival of approximately 1 year [5].

Carfilzomib was given using a step-by-step dosing scheme conceived to minimize toxicity: a 20 mg/m2 dose was used in the first cycle together with premedication and dexamethasone hydration; the dose was then increased to 27 mg/m2 in the second cycle, if tolerated [6]. For the most part, carfilzomib was relatively well tolerated indeed, the most frequent adverse effect being nausea, anemia and thrombocytopenia; peripheral neuropathy was rare [7]. Nevertheless, 11 patients (4.1%) died within administration of first two cycles 2 due to toxicity, including 2% who died of various organs failure. This was probably due to the use of lower, less effective doses in the first cycle, advanced disease and very early evaluation of response. Twenty-three percent of the patients discontinued carfilzomib within the first two cycles because of disease progression [8]. However, the FDA has recently approved carfilzomib for patients with progressive disease during or after bortezomib and IMiD [6, 9].

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Experimental part

Subjects and methods

Sampling and representativeness

The study was conducted on a group of 105 patients admitted to the Hematology Department of the Municipal Emergency Clinical Hospital of Timisoara from 01 January 2013 until 31 December 2017. The study is retrospective for the period 2013-2015, so that medical records of patients admitted and diagnosed for the first time with multiple myeloma during that period were analyzed. The study became prospective starting with 2015 year and we included patients admitted to our clinic for a first diagnosis (table 1).

Table 1
BASELINE CHARACTERISTICS

Parameter		Bortezomib+dexamethasone	Carfilzomib+dexamethasone
Age	<40 years	1 [3.7%]	0
	41-60 years	10 [37%]	13 [65%]
	61-75 years	15 [55.6%]	7 [35%]
	>75 years	1 [3.7%]	0
Sex	male	10 [37%]	10 [50%]
	female	17 [63%]	10 [50%]
Stage	I	6 [22.2%]	1 [5%]
	II	4[14.8%]	4 [20%]
	III	17[63%]	15 [75%]

The 105 patients underwent first line treatment for multiple myeloma. Following first-line treatment, 27 of the patients experienced partial remission and 32 progressive disease. They were assigned to second treatment regimens, as follows: 27 of them received bortezomib and dexamethasone, while 20 received carfilzomib and dexamethasone. Twelve patients received other therapeutic regimens.

The protocol for bortezomib treatment was:

-Bortezomib 1.3mg/m^2, days 1,4, 8, 11

-Dexamethasone 40mg daily, days 1-2, 4-5, 8-9, 11-12

The treatment cycle was repeated at 21 days.

For the group receiving carfilzomib associated with dexamethasone, the treatment protocol was the following:

Carfilzomib is administered intravenously as a 30-minute infusion over two consecutive days, each week for three weeks (days 1, 2, 8, 9, 15 and 16) followed by a 12-day rest period (days 17-28). Each 28-day interval is considered a treatment cycle. Carfilzomib is given at the starting dose of 20 mg/m2 (maximum dose 44 mg) on days 1 and 2 of the treatment cycle 1. If tolerated, the dose should be increased to 56 mg m2 (maximum dose 123 mg) on the 8^{th} day of the first treatment cycle. Dexamethasone is administered as 20 mg oral or intravenous dose on days 1, 2, 8, 9, 15, 16, 22 and 23 of the 28-day treatment cycles. Dexamethasone should be given 30 minutes to 4 hours before Carfilzomib.

Statistical analysis

The data were collected from the medical records for each patient. Anthropometric parameters, disease stage, adverse events, type of treatment and response to treatment were analyzed. Statistical data processing was performed with the SPSS20.0 program. For descriptive statistics, the results were expressed in percentages and absolute values. Kaplan Meyer analysis was used to plot the survival curve in the two groups.

Results and discussions

For the second treatment line, in which patients with partial remission and progressive disease [59 patients] were included, two groups were created: one group, comprising 27 patients, received bortezomib and dexamethasone, whereas the other group, which included 20 patients, received carfilzomib and dexamethasone. Twelve patients received other regimens.

Most patients treated with bortezomib and dexamethasone were aged 61 to 75 years (55.6%), followed by the 41-60 age groups (37%). Only 3.7% of the patients were either under 40 or over 75 years of age. Women (63%) prevail in this group, most patients being diagnosed stage III.

In the Carfilzomib group, most patients (65%) were in the 41 - 60 age group, with equal gender distribution. Most patients (75%) had stage III disease at the time of diagnosis, 20% had stage II and only 5% had stage I.

The rate of complications in the two groups is similar, with a higher proportion of anemia in patients treated with bortezomib and less bone pain and pathological fractures in patients treated with carfilzomib (table 2). There was no statistically significant difference between the two groups regarding the frequency of complications.

Table 2
ADVERSE EVENTS

	Bortezomib+ dexamethasone Events/number	Carfilzomib+ dexamethasone Events/number	p-value
Anemia	12/27	7/20	0.839
Thrombocytopenia	7/27	3/20	0.659
Hypercalcemia	6/27	6/20	0.050
Infections	4/27	2/20	0.881
Myelosuppression	5/27	2/20	0.702
IRC	6/27	7/20	0.625
Hyperviscosity syndrome	2/27	2/20	0.745
Bone pain	6/27	8/20	0.212
Bone marrow compression	2/27	3/20	0.200

Treatment response in the two groups was dissimilar. In the case of bortezomib group, a higher percentage of patients with progressive disease after the second cycle of treatment is observed, unlike the carfilzomib group. Treatment response is shown in Table 3.

Table 3
TREATMENT RESPONSE

		Bortezomib+ dexamethasone	Carfilzomib+ dexamethasone
Response	RP	6 [22.3%]	7 [35%]
	RC	8[29.6%]	4[20%]
	BS- plateau phase	5[18.5%]	4[20%]
	BP	8 [29.6%]	5[25%]

The survival mean (Table 4) is higher in the group of patients treated with bortezomib that in that of patients receiving carfilzomib, 37 months versus 34 months (fig 1).

Table 4
MEAN SURVIVAL TIMES

	Mean[a]			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
bortezomib	37.074	3.790	29.645	44.503
carfilzomib	34.850	3.469	28.051	41.649
Overall	27.667	1.756	24.225	31.109

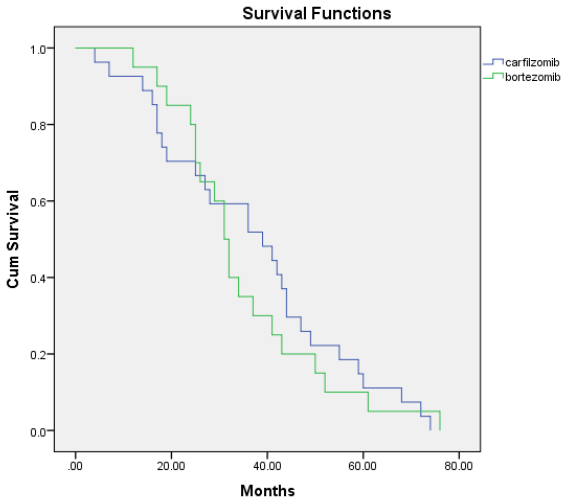

Fig. 1. Cumulative survival

The ENDEAVOR study was considered the first phase 3 comparison study between the two proteasome inhibitors in patients with relapsed or refractory myeloma. The ENDEAVOR study provides important information on the relative efficacy and safety of these two proteasome inhibitors, as well as regarding the progression-free survival in patients treated with bortezomib and dexamethasone compared with those treated with carfilzomib and dexamethasone. Unlike bortezomib, carfilzomib is an irreversible proteasome inhibitor triggering sustained proteasome inhibition. As revealed in preclinical

studies, carfilzomib is a more powerful inhibitor than bortezomib in multiple myeloma cell lines. [10] In our study we included 27 patients receiving bortezomib and dexamethasone, and 20 patients treated with carfilzomib and dexamethasone. The age of patients in the two groups was 40 to 75 years, most of them having stage III disease. The 47 patients included in the two groups of second line treatment had relapsed or progressive disease. When assessing the adverse events following the bortezomib and dexamethasone treatment, unlike the clinical trials where the most frequent adverse event was peripheral neuropathy [11,12,13], in our study the most frequent adverse event in this group was anemia, while in the group treated with carfilzomib and dexamethasone were bone pain or pathological fractures. Other studies have reported as frequent adverse events hypertension and heart failure [14], which were not encountered in our study. However, kidney failure reported in phase II and III studies was also seen in our study in both groups of patients.

Phase 3 randomized studies have shown that patients treated with carfilzomib and dexamethasone had higher progression-free survival than those treated with bortezomib and dexamethasone. Nevertheless, neither of the proteasome inhibitors appeared to significantly outweigh the poor prognosis of high-risk patients; in both treatment groups, patients with high-risk cytogenetics had lower progression-free survival than the overall population. Progression-free survival was also longer in patients in the carfilzomib group than in those in the bortezomib group, regardless of their transplant status; the difference between treatment groups was lower in patients with a prior transplant compared to those without a transplant, probably because the former patients are more difficult to treat due to the transplant-related toxic effects. The proportion of patients who achieved a good response in the carfilzomib group was greater than that in the bortezomib group, while the carfilzomib group had a longer mean response time, as the ENDEAVOR study showed. The fact that the proportion of patients with complete response or better and very good partial response was higher in the carfilzomib group than in the bortezomib group was encouraging, because other studies showed an association between the quality of response and improved survival in patients with multiple myeloma [15]. In our study, probably because of the small number of patients, the response to treatment is slightly better for the bortezomib-treated group.

In the bortezomib group, median progression-free survival was consistent with historical data from phases 2 and 3 of clinical trials [16-18] assessing bortezomib and dexamethasone in patients with recurrent or refractory multiple myeloma (median progression-free survival, 3 · 8-11 · 9 months). In the present study, the mean survival was higher in the bortezomib and dexamethasone group than in carfilzomib and dexamethasone group.

Conclusions

In conclusion, the results of our study show that patients with relapsed or refractory myeloma who received carfilzomib had clinically significant improvements in overall survival and good treatment responses comparable to patients receiving bortezomib. Severe adverse events were similar in patients receiving both carfilzomib and bortezomib. Therefore, carfilzomib should be considered a viable treatment option as standard of care in patients with recurrent or refractory multiple myeloma.

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