Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study

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ABSTRACT

Background: Treatment of multiple myeloma (MM) has evolved considerably in the past few years with availability of several news drugs as well as increasing use of multidrug combinations. These changes have led to the improved survival seen among patients with MM. We have previously shown that outcomes of patients intolerant or refractory to one of the immunomodulatory drugs (IMiDs) and bortezomib had a poor outcome. Since that time, other drugs of the same class as well as new classes of drugs have been introduced for the treatment of MM. We designed this retrospective study to estimate the outcomes in patients with relapsed myeloma, who have become refractory to the current generation IMiDs and proteasome inhibitors (PIs).

OBJECTIVES

We undertook the current multicenter, retrospective study, to obtain a real world assessment of the outcomes of patients who have received

(i) at least 3 prior lines of therapy

(ii) were refractory to both an IMiD (lenalidomide or pomalidomide) AND a PI (bortezomib or carfilzomib), and

(iii) exposed to an alkylating agent

METHODS

Patients with relapsed MM who have received at least 3 prior lines of therapy, is refractory to both an IMiD (lenalidomide or pomalidomide) AND a PI (bortezomib or carfilzomib), and has been exposed to an alkylating agent were identified from multiple centers. The time patients met the above criteria was defined as time zero (T_0), and details of all treatment regimens before and after T_0 were collected using electronic CRFs. The study was approved by the IRB at the respective centers.

CONCLUSIONS

The study provides the expected outcome following development of MM that is refractory to a PI and an IMiD. The outcomes of these patients appear to be better than we had seen historically in patients refractory/ intolerant to bortezomib and IMiDs, highlighting the increased treatment options available for these patients. However, there is decreasing response rate to sequential regimens highlighting the development of drug resistance. The data provides a bench mark for comparison of new therapies that are currently being evaluated.

RESULTS

- 543 patients were enrolled in this study; median (range) age was 62 years (31-87) and 61% were males. Patients were enrolled from centers in North America (n=181), Europe (n=318), and Asia Pacific (n=44).
- Patients were diagnosed between 2006 and 2014, the median (range) duration between diagnosis of myeloma and study entry (T_0) was 3 years (0.3 to 9). The median (95% CI) estimated follow up from diagnosis and from T_0 were 61 (57, 66) months and 13 (11, 15) months respectively. The median (range) number of lines of therapy prior to T_0 was 4 (3-13), 48% had a prior transplant. The median (95% CI) OS from T_0 for the entire cohort was 13 (11, 15) months.
- 462 (74%) patients had at least one regimen recorded after T_0, and the median (range) number of recorded regimens was 2 (1-9). Nearly a quarter of the patients received a PI containing regimen; 81 patients (7.5%) with bortezomib and carfilzomib in 38 (8%) as their initial regimen post-T_0.
- An IMiD was part of the initial regimen after T_0 in 274 (59%) patients, including 11% with lenalidomide, 39% with pomalidomide and 10% with thalidomide.
- Alkylating agents (cyclophosphamide, melphalan, or bendamustine) were commonly employed at this stage of the disease with 173 (37%) patients receiving a regimen that contained one of these drugs.
- The median (95% CI) OS for the entire cohort was 13 months (11, 15) from T_0. The median (95% CI) PFS, and OS from T_0 was 5 (4, 6), and 15 (13, 17), respectively. The overall survival for the 81 patients with no treatment post T0 was only 2 months.

Table: Best response to regimen, by regimen number, for the regimens following T_0

Regimen	1st	2nd	3rd	4th	5th
Number of patients	462	264	137	68	42
Best response (>=PR) %	153 (33.1)	65 (24.6)	36 (26.3)	20 (29.4)	6 (14.3)
Best response (>=MR) %	156 (33.8)	65 (24.6)	36 (26.3)	20 (29.4)	6 (14.3)
CR/sCR	8 (1.7)	3 (1.2)	3 (2.2)	1 (1.5)	0 (0.0)
VGPR	44 (9.5)	17 (6.5)	8 (5.8)	2 (3.0)	1 (2.4)
PR	101 (21.9)	45 (17.1)	25 (18.2)	17 (25.0)	5 (11.9)
MR	3 (0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
SD	159 (34.4)	114 (43.2)	53 (38.7)	23 (33.8)	17 (40.5)
PD	146 (31.6)	85 (32.2)	46 (33.6)	26 (38.2)	19 (45.2)
Best Response (>=PR) with a regimen with bortezomib, len or thal	56 (12.1)	26 (9.8)	14 (10.2)	7 (10.3)	2 (4.8)
Best Response(>=PR) with a regimen with carfilzomib or pomalidomide	73 (15.8)	25 (9.5)	16 (11.7)	7 (10.3)	2 (4.8)
Median duration of treatment (mos.)	2.8	2.4	2.2	2.2	1.8

- In a multivariate analysis, duration from diagnosis to T0, ISS stage III and number of lines of therapy were all associated with inferior PFS, as well as OS, and in addition, serum creatinine>2 mg/dL at T_0 also predicted inferior OS.

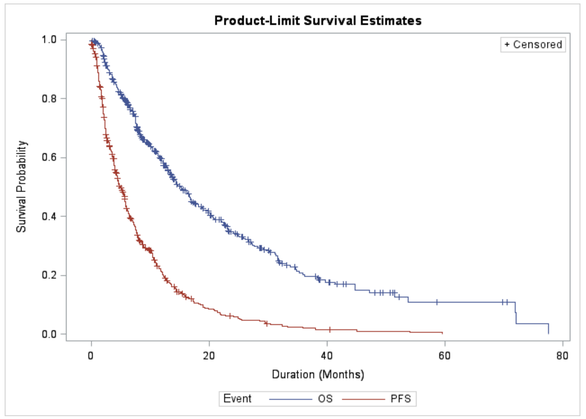
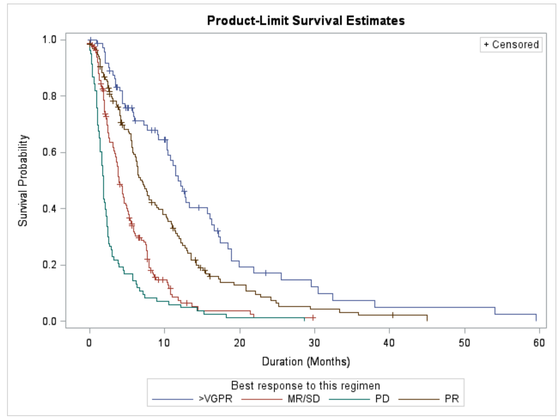


Figure : PFS and OS from T0 for patients receiving a therapy post T0



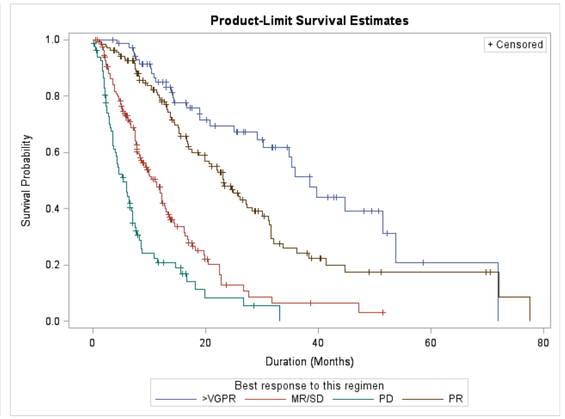


Figure : PFS (a) and OS (b) from T0 for patients receiving a therapy post T0 based on depth of response to first regimen given post T0