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Response to salvage therapies and outcome in patients with multiple myeloma relapsing after pomalidomide therapy

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Significant advances have been made in the therapeutic landscape of Multiple Myeloma (MM) in the past decade with the introduction of novel therapies such as thalidomide, lenalidomide and the proteasome inhibitor bortezomib.[1–3] These drugs have improved survival in MM, but without a definite cure.[4] Pomalidomide is the newest immunomodulatory drug to be evaluated in clinical trials and has shown considerable efficacy.[5,6] Phase I/II trials of pomalidomide combined with low-dose dexamethasone have reported partial response (PR) rates of 29–63% in relapsed MM, including in patients refractory to other IMiDs or bortezomib.[7–10] It is not clear how patients respond to existing therapies, once the disease becomes refractory to pomalidomide. We examined this question among patients receiving pomalidomide therapy in a phase 2 trial.

Patients enrolled in an ongoing phase 2 trial of pomalidomide and dexamethasone for relapsed myeloma, who subsequently have gone off study for disease progression, form the study population.[7,8] Several cohorts of patients ($\geqslant 3$ prior therapies not specified, lenalidomide refractory and lenalidomide and bortezomib refractory patients) were enrolled sequentially in this trial.[7,11] Details of subsequent therapies and survival data were obtained from medical records. Approval from the Mayo Foundation Institutional Review Board was obtained in accordance with federal regulations and the Declaration of Helsinki.

Response to therapy was assessed using the International Myeloma Working Group (IMWG) uniform response criteria. The χ^2 and Fisher's exact tests were used to compare differences between nominal variables and the Mann–Whitney *U*-test or Kruskal–Wallis test were used for continuous variables. Kaplan–Meier analysis was used to estimate survival, and differences between survival curves were tested for statistical significance using log-rank test.

A total of 74 patients from among 183 patients who had relapsed after pomalidomide were included in the study. The median age at the time of progression on pomalidomide was 63 (range: 39–89) years; 72% (53) were male. The median duration of pomalidomide therapy was 4.3 (range: 1–22) months and time from diagnosis to progression on pomalidomide was 5.0 (0.5–14) years. At the time of study entry, 61 (82%) patients were lenalidomide refractory, 39 (53%) patients were bortezomib refractory and 37 (50%) were refractory to both lenalidomide and bortezomib. The best confirmed response to pomalidomide was a PR or better in 21 (28%) patients and Minor Response (MR) or better in 37 patients (49%) in the study cohort. These results are in accordance with what has been reported before.[7,11]

At least one treatment was recorded for 52 (70%) patients following progression on pomalidomide. The most commonly used regimen following progression on pomalidomide contained bortezomib, including bortezomib with dexamethasone, with or without cyclophosphamide or melphalan (24; 46%). Overall, 24 patients had an MR or better (44%), including 16 (31%) patients with a PR or better to first therapy following relapse on pomalidomide (Table 1). These response rates are similar to what has been described in patients refractory to bortezomib and either thalidomide or lenalidomide in a multicenter study from IMWG.[12] Among the four patients receiving autologous stem cell transplantation (ASCT) as first therapy following progression on pomalidomide, three had a PR or better. An objective response of PR or better was seen in 6 (25%) patients treated with bortezomib-based regimen. Among the other regimens, lenalidomide-based regimens were instituted in seven patients; alkylator–steroid combination and VDT-PACE being employed in seven and six patients, respectively, achieving a confirmed response of PR or better in a third of the patients. The salvage regimens used in these patients reflect the current practice with many of the newer drugs being repeated. Previous studies have demonstrated that retreatment with bortezomib or IMiDs in patients previously exposed to these agents can be associated with clinically meaningful responses.[13,14] Patients experiencing relapse after long interval are likely to respond to same or similar regimens. For patients who have only a brief period of control, use of drugs with different mechanisms of action may overcome drug resistance to some extent.

Overall, 120 regimens were employed across 52 patients following progression on pomalidomide; median (range) number of regimens per patients was 1 (0–8). The response rates to the different regimens are shown in Table 1. The most commonly used regimen was bortezomib-based in 43 (36%); followed by ASCT in 15 (13%), alkylator-steroid combination in 15 (11%), VDT-PACE in 14 (12%), and lenalidomide-based in

Table 1 Response to first salvage regimen and all regimens after progression on pomalidomide

Regimen	*Response to first salvage regimen after pomalidomide*				*Response across all regimens following pomalidomide*			
	*Patients (*N*)*	*SD or Prog* N *(%)*	*MR* N *(%)*	*⩾PR* N *(%)*	*Lines of therapy (*N*)*	*SD or Prog* N *(%)*	*MR* N *(%)*	*⩾PR* N *(%)*
ASCT	4	1 (25)		3 (75)	15	1 (6)		12 (80)
Bz-based	24	13 (58)	3 (13)	6 (25)	43	24 (56)	4 (9)	12 (28)
Len-based	7	5 (71)		2 (29)	13	8 (62)		2 (13)
Carfilzomib	2	1 (50)	1 (50)		3	2 (67)	1 (33)	
Alk + Steroid	7	2 (29)	2 (29)	2 (29)	15	5 (33)	3 (20)	4 (27)
VDT-PACE	6	3 (50)	1 (16)	2 (33)	14	5 (36)	5 (36)	4 (28)
Steroid	0				3	1 (33)		1 (33)
VRD	0				3		2 (66)	
Other	2		1 (50)	1 (50)	11	8 (73)		3 (27)

Abbreviations: MR, minimal Response; PR, partial Response; Prog, Progression; SD, Stable Disease.
Lines of therapy: Number of times the particular modality of therapy was instituted following progression on pomalidomide; regimens: ASCT: autologous stem cell transplantation, Bz: Bortezomib, Len: Lenalidomide, Alk: Alkylator, VDT-PACE: Velcade (Bortezomib), Dexamethasone, Thalidomide, Cisplatin, Adriamycin, Cyclophosphamide, Etoposide and VRD: Velcade(Bortezomib), Revlimid(Lenalidomide), Dexamethasone (Steroid).

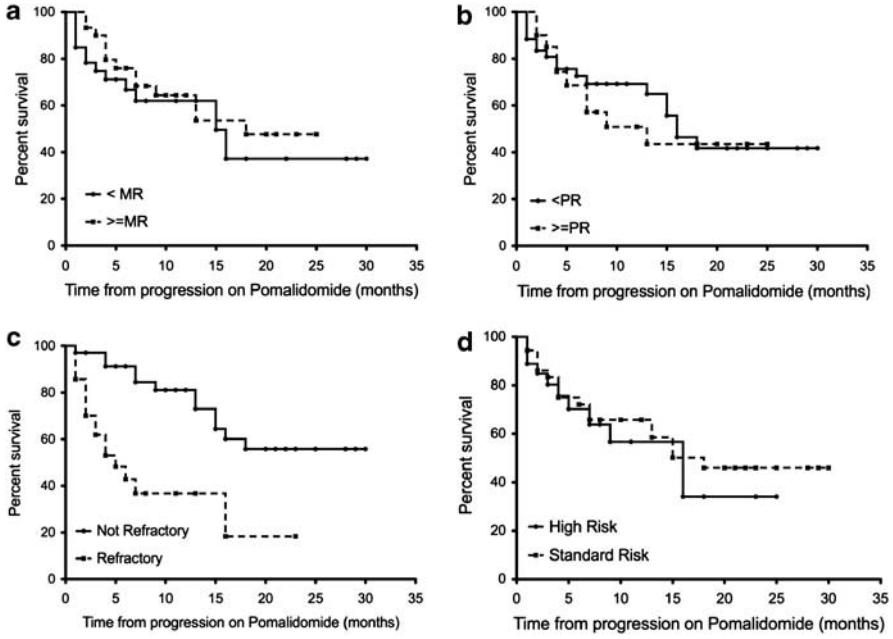

Figure 1 (**a**) Kaplan–Meier curves demonstrating the OS from the time of progression on pomalidomide, based on response to pomalidomide (MR) or better versus <MR. Survival curves were compared using the log-rank tests; $P=0.88$. (**b**) Kaplan–Meier curves demonstrating the OS from the time of progression on pomalidomide based on response to pomalidomide (PR) or better and versus <PR. Survival curves were compared using the log-rank tests; $P=0.8$. (**c**) Kaplan–Meier curves demonstrating the OS from the time of progression on pomalidomide based on relapse category; lenalidomide and bortezomib refractory versus the rest. Survival curves were compared using the log-rank tests; $P<0.05$. (**d**) Kaplan–Meier curves demonstrating the OS from the time of progression on pomalidomide based on cytogenetic and FISH-based risk classification. Survival curves were compared using the log-rank tests; $P=0.4$.

13 (11%) patients. The highest rate of objective response of PR or better (80%) was seen in patients treated with ASCT. The majority of these patients, 11 (73%) were undergoing a salvage second ASCT, having collected stem cells early on in the course of their disease. For the remaining four patients, this was their first ASCT, and all of the patients had a PR or better after ASCT. These findings reflect the increasing shift in practice of using ASCT later in the course of disease. Lenalidomide-based regimens were employed 12 times, with the best response being PR in two and SD in five patients. This likely reflects non-cross resistant mechanisms of action and is similar to the 30% response rate seen with pomalidomide in lenalidomide refractory patients. Overall, a confirmed response of PR or better was achieved in 27% of patients receiving other therapies.

The median overall survival (OS) from the time of progression on pomalidomide was 13.2 months (95% CI; 6, NR). The OS was similar between those patients who had a response to pomalidomide (MR or better) and those who did not (Figure 1a; $P=0.88$), as well as those with PR or better compared with the rest (Figure 1b; $P=0.80$) However, the OS was shorter for patients who were refractory to lenalidomide and bortezomib at study entry (3.3 months; 95% CI, 1.1, 5.7) compared with the rest (median not reached); (Figure 1c; $P<0.001$). This likely reflects acquired drug resistance in the heavily pretreated dual refractory patients. Several mechanisms have been implicated in acquired drug resistance in myeloma; including overexpression of P-glycoprotein causing reduction in intracellular drug concentration, changes in cellular drug targets, chromosomal

aberrations, altered drug metabolism, and enhanced cellular repair processes. In contrast, the median OS for the 14 patients undergoing an ASCT was not reached, suggesting perhaps continued response to alkylator-based therapy.

Among the 74 patients, 31 had high-risk disease based on the presence of one or more of the following abnormalities (Del 13 by metaphase cytogenetics, hypodiploidy, del 17p, t(4;14) or t(14;16)). The median OS from the time of progression was 9.5 months for the high-risk group compared with 14.7 months for the rest; $P=0.4$. The higher than average proportion of patients with high-risk disease likely reflects a selection bias in favor of patients relapsing rapidly after currently available treatments.

Our study represents a unique description of response to salvage therapies and outcome of patients progressing on pomalidomide, the latest IMiD to reach clinical trials. Several important conclusions can be derived from these clinical results. It confirms poor outcome of the patients relapsing after novel therapies. We also provide evidence of retained activity of lenalidomide in a proportion of patients relapsing on pomalidomide, suggesting that a trial of lenalidomide in these patients is justified. Finally, even in this relapsed and refractory population, ASCT when feasible is associated with high response rates.

Conflict of interest

MQL has received research funding from Celgene; JM has receivedresearch funding from Celgene, Onyx, Novartis; AD has received research funding from Celgene and Travel award binding site; MAG has received Honoraria from Celgene, Millenium, Neotope Eisai, Inc., Lilly Research Laboratories, Optum Health Education, Research to Practice, Physician's Education Resource and Amgen, Inc.; and SKK has received research funding from Celegene, Genzyme, Millenium, Novartis, Bayer, Merck and Cephalon, and has participated in Advisory board for Genzyme. The remaining authors declare no conflict of interest.

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Phase 1b trial of atacicept, a recombinant protein binding BLyS and APRIL, in patients with chronic lymphocytic leukemia

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Chronic lymphocytic leukemia (CLL) is a common form of leukemia in the Western world, with an incidence rate of 5/100 000, and predominantly occurs in older people, with a median age at diagnosis of 70 years. This group of patients often does not qualify for intense combination chemotherapy, thereby stressing the need for alternative treatment options. CLL is mostly characterized by accumulation of malignant B-cells