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Long-lasting Responses to Immunomodulatory Drugs (IMIDs) in Combination with Dexamethasone in Multiple Myeloma; Identification of Exceptional Responders at any Treatment Line

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Abstract

Background: There is a growing interest in the study of patients that achieve exceptionally long-lasting remissions although suffering from incurable neoplastic disorders. This is the case for multiple myeloma (MM), the treatment of which has greatly improved with the emergence of new, biology-driven modalities that prolonged survival. The identification of "exceptional responders" to basic treatment such as immunoregulatory drugs (IMIDs) and dexamethasone could eventually reveal a small proportion of patients potentially curable with more drugs combinations.

Aims: To investigate MM exceptional responders to IMiDs.

Objectives: To identify exceptional responders among all patients with symptomatic MM treated either at diagnosis or in relapse with an IMID (thalidomide, lenalidomide, pomalidomide) in combination with dexamethasone and to study their clinical characteristics and survival.

Materials and Methods: A cohort of 164 patients was studied. "Exceptional responders" were defined as patients that remained in remission for at least 72 months after 1st line treatment, 60 months after 2nd line, 42 months after 3rd to 6th line and for at least 30 months beyond 6th line. Statistical analysis was performed using the SPSS v.24.0 software. Survival was evaluated by the log rank test.

Results: Thirty-one (19%) exceptional responders were detected, of whom 11 (15%) out of 75 received thalidomide/dexamethasone (TD), 18 (14%) out of 132 lenalidomide/dexamethasone (LD) and 2 (25%) out of 8 pomalidomide dexamethasone (PD). The median number of treatment lines received prior to TD, LD and PD treatment was 2, 2 and 7 respectively. Exceptional responders' survival from TD, LD and PD treatment to last follow-up or death was 85, 73 and 35 months while their overall survival was 95, 94,5 and 149 months respectively.

Seventeen patients are alive and 4 disease-free. They did not exhibit specific clinical or biochemical profile beside the absence of hypercalcemia and extramedullary disease at treatment initiation.

Conclusion: We identified exceptional responders to IMIDs-based treatment, their further examination may enlighten on disease biologic aspects that could open the way to cure.

Keywords: Multiple myeloma; Immunomodulatory drugs; Thalidomide; Pomalidomide; Lenalidomide; Exceptional responders

Abbreviations: MM: Multiple Myeloma; VAD: Vincristine- Anthracyclin- Dexamethasone; ASCT: Autologous Stem Cell Transplantation; IMIDs: Immunomodulatory Drugs; b2M: beta-2 Microglobulin; FLCR: Free Light Chains Ratio; FISH: Fluorescent in Situ Hybridization; TTP: Time to Progression; TD: Thalidomide/ Dexamethasone; LD: Lenalidomide/ Dexamethasone; PD: Pomalidomide Dexamethasone; SCR: Stringent Complete Remission; CR: Complete Remission; MGUS: Monoclonal Gammopathy of Undetermined Significance

Introduction

Multiple Myeloma (MM) is a plasma cell disorder characterized by clonal, usually paraprotein-secreting, plasma cell proliferation in the bone marrow. In the presence of disease related symptoms (CRAB), treatment is immediately required to avoid end organ damage. The management of symptomatic multiple myeloma (MM) patients have changed dramatically during the last years. Before 2000, with melphalan-prednisone or VAD (vincristine-anthracyclin-dexamethasone) regimen plus or minus high dose chemotherapy with autologous stem cell transplantation (ASCT), patients' median survival was 3 - 5 years. Hopefully, new agents steadily emerged since the new century; thalidomide, bortezomib and lenalidomide became consecutively available for the treatment of relapsed/refractory MM patients in 2000, 2004 and 2007 respectively, while the two first were approved for induction treatment in 2008 and the last in 2015. With these new agents, patients' overall survival improved [1].

However, the disease remains incurable. Patients relapse after a varying period of time, possibly respond again to another treatment, then relapse again and so on. It was shown that the duration of response to each treatment line is inversely related to the number of previous lines [2]. Refractoriness develops over disease course possibly because of the emergence of new clones [3]. More recently, next generation proteasome inhibitors such as carlfizomib or ixazomib and immunomodulatory drugs (IMIDs) such as pomalidomide, have been approved, as well as monoclonal antibodies (elotuzumab, daratumumab) and histone deacetylase inhibitors (panobinostat). Proteasome inhibitors and/or IMIDs have become the matrix that, in combination with dexamethasone and/or another class of drugs, are administered to MM patients in an intend to treat and, if ever possible, to cure [4]. Best qualitative responses [5-7], non-high-risk prognostic factors and disease characteristics as well as continuous treatment contribute to increased longevity [8,9]. A growing interest in identifying exceptional responders to therapy in terms of duration, response and molecular characteristics has initiated [10,11]. It is tempting to assume that long-lasting responders to IMID in combination with dexamethasone are the ones that could eventually be cured, especially if they were offered additional agents with another mode of action. We therefore aimed to characterize exceptional responders in a series of symptomatic MM patients treated with an IMiDs (thalidomide, lenalidomide, pomalidomide) in combination with dexamethasone.

Patients and Methods

We retrospectively reviewed the medical records of all patients with symptomatic MM diagnosed and followed-up in our department and treated with IMIDs in combination with dexamethasone at any treatment line, according to institutional practice and current drug approvals. Clinical reports, laboratory results including complete blood counts, renal and hepatic function tests, serum calcium, LDH, beta-2 microglobulin (b2M), protein electrophoresis and immunofixation, quantitative immunoglobulin measurements including free light chains and their ratio (FLCR), and skeletal imaging were collected. The type and line of treatment and the response obtained were recorded; time to progression was calculated. Bone marrow studies including the evaluation of plasma cell infiltration in smears and biopsy in all patients and fluorescent in situ hybridization (FISH) results for t (4;14), t(14;16) and del17p as well as conventional metaphase karyotyping analysis, when available, were included in the database. Informed consent was obtained from all patients. Based

on Vu, et al. [10] study where patients with at least 72 month time to progression (TTP) after 1st line treatment, were considered "exceptional responders" because 72 months approximatively correspond to" three times the TTP expected with primary Rd" and because time to progression (TTP) steadily decrease after each subsequent relapse [2], we defined "exceptional responders" as patients that remained in remission for at least 6 years (72 months) after 1st line treatment, at least 5 years (60 months) after 2nd line, 3 years and a half (42 months) after 3rd line and up to 6th line and for at least 2 years and a half (30 months) beyond 6th line.

Median FLCR in the whole series was 42 and used as cut-off value. Statistical analysis was performed using the SPSS v.24.0 software. The χ2-test was used to compare nominal values. Survival was evaluated by the log rank test.

Results

There were 164 symptomatic multiple myeloma patients treated with IMIDs in combination with dexamethasone, of whom 75 received thalidomide/dexamethasone (TD), 132 lenalidomide/dexamethasone (LD) and 8 pomalidomide dexamethasone (PD). Patients were followed from diagnosis and all over their disease course. The median number of treatment lines they received was 4, and some of the patients received consecutively all 3 IMIDs. The median follow-up time of the whole cohort was 64 months (2-332). Thirty-one (19%) were identified as exceptional responders; 11 (15%), 18 (14%) and 2 (25%) were treated with TD, LD, CR and PD respectively

Exceptional responders' characteristics at the time of treatment initiation are summarized in Table 1. Thalidomide dosage ranged from 100 to 400 mg/day, lenalidomide was prescribed at 25mg per os daily and pomalidomide at 4mg daily during 21 days of a 28 days cycle. In all patients, dexamethasone dosage was usually 40mg or 20mg (depending on age) weekly or at days 1, 10 and 20 of the cycle. IMIDs dose reduction was needed in few cases due to side effects, (mainly fatigue, diarrhea and neutropenia).

Findings at Treatment Initiation		**TD**	**LD**	**PD**
Exceptional responders	n=31	n= 11	n=18	n=2
Age, years, median (range)	64 (30-85)	63,5 (30-81)	66 (48-84)	73 (61-85)
Sex Male	17 (53%)	7	9	1
Female	14 (47%)	4	9	1
MM type IgG	17 (55%)	6(19,5%)	9	2
IgA	7 (22,5%)	2	5	-
LC	6 (19,5%)	3	3	-
IgD	1 (3%)	-	11 (3%)	-
Hb ≤ 10 g/L		2	2	0
Cr ≥ 2mg/dl		2	2	1
Increased Ca		0	0	0
Elevated LDH		1	1	1
B2M ≥ 3,5 mg/dl		7	12	2
FLCR > median		2	7	1
Symptomatic bone disease		1	2	0
PCBM >60%		7	12	2
Extramedullary disease		0	0	0
Number of previous treatment lines 1		1	0	0
2		8	9	0
3		2	5	0
4		0	2	0
5		0	1	0
6		0	1	0

7	0	0	1
8	0	0	1
ASCT after IMID treatment	1	0	0
TFDT, median (range), months	17 (0-131)	27,5 (5-105)	115,5 (80-151)

TD: Thalidomide/Dexamethasone, LD: Lenalidomide/Dexamethasone, PD: Pomalidomide/Dexamethasone, LC: light chain only, Hb: Hemoglobin, Ca: calcium, PCBM: plasma cell bone marrow infiltration, FLCR: free light chain ratio, ASCT: Autologous stem cell transplantation, TFDT: time from diagnosis to treatment

Table 1: Patients' Characteristics at Treatment Initiation.

In exceptional responders of the TD group, conventional karyotype was available in 6 patients and FISH assessment of adverse genetic markers in two at treatment initiation; only one patient displayed t (14;16). In LD group of exceptional responders, karyotype was available in 12 patients and FISH studies were performed in 4; aberrations were observed only in 1 patient with add 14q32 and in another with t (1;7).

The depth of response to IMID treatment is shown in Table 2, as well as median time to next treatment and overall survival, that was prolonged. Seventeen exceptional responders are alive, 6 in TD, 9 in LD and 2 in PD arm respectively. Four patients are in sustained remission without any evidence of disease, 2 treated with TD and 2 with LD; all 4 were in second line and achieved sCR (stringent complete remission).Preceding neoplastic disorders consisted in chronic lymphocytic leukemia in one patient treated with TD and in chronic myeloid leukemia and Monoclonal gammopathy of undetermined significance in another that received LD. One patient developed lung cancer and another breast cancer while under LD treatment, both in MM CR. A third patient developed stomach cancer, immediately after MM relapse.

Treatment		TD	LD	PD
Response	sCR	2	3	0
	CR	2	4	0
	VGPR	1	7	2
	PR	6	4	0
TTNT, median (range), months		75 (49-188)	52 (43-110)	32 (31-33)
Time from treatment to last FU, months		85 (49-188)	73 (43-110)	35 (33-37)
OS, median (range), months		95 (74-208)	94,5 (54-178)	149 (116-182)

TD: Thalidomide/Dexamethasone, LD: Lenalidomide/Dexamethasone, PD: Pomalidomide/Dexamethasone, sCR: stringent complete remission, CR: complete remission, VGPR: very good partial remission, PR: partial remission, TTNT: time to next treatment, FU: follow-up, OS: overall survival

Table 2: Quality of Response and Follow-up of Exceptional Responders.

Discussion

IMiDs display pleiotropic antimyeloma properties such as immunomodulation, anti-angiogenic, anti-inflammatory and anti-proliferative effects, as well as down regulation of biologically significant microenvironmental cytokines [12]; thus, this class of drugs can target both the malignant plasma cells and its microenvironment. In addition, they can be easily and relatively safely [13] administered per os, continuously [14], in an outpatient basis rendering them very attractive. Long term benefit of IMIDs/dexamethasone treatment in myeloma has been previously evaluated, although it mostly concerned lenalidomide/ dexamethazone induction [13-15] or second line treatment [16]. One step further, Vu T, et al. [10] presented a series of 33 out of 240 (14%) patients that received lenalidomide/dexamethasone as first line and remained in remission for 6 years (72 months) or more. These exceptional responders received lenalidomide/dexamethasone until progression (9 patients), completely stopped treatment (11 patients), received ASCT (8 patients) or restarted at relapse (5 patients) and half of them remained disease-free beyond 6 years. Myeloma defining event was mostly bone disease, all patients had normal renal function and an increased frequency of trisomies were observed in karyotype. However, exceptional responders presented anemia, increased LDH, hypercalcemia, increased beta-2-microglobulin or FLCR at a varying percentage,

meaning that these common adverse prognostic factors were overcame. Interestingly CR was not achieved by all patients. The authors concluded that they believe that these patients will behave indolently even after relapse. Here, we possibly confirmed this statement. We studied exceptional responders to IMIDs/dexamethasone treatment at any line. In our study none of the patients that received lenalidomide/dexamethasone were in first line because six years have not passed since its approval at induction in 2015; pomalidomide can be only given at 3rd line and beyond. Only thalidomide/ dexamethasone could be prescribed at first line to some patients. Likewise, we reviewed the files of 164 MM patients treated with IMIDs/ dexamethasone, and identified 31 exceptional responders, of whom 11 were treated with thalidomide/ dexamethasone, 18 with lenalidomide/ dexamethasone and 2 with pomalidomide/ dexamethasone. In our series, in keep with Vu et al anemia, increased LDH, FLCR or beta 2 microglobulin were present at various percentage at treatment initiation; on the contrary, none had hypercalcemia and some presented renal failure. Exceptional responders were encountered as far as the 8th treatment line, meaning that there is a subset of myelomas that keeps an indolent behavior for a long time. In agreement with Vu T, et al. [10] complete responses were not mandatory for sustained remissions but it should be mentioned that the four patients that are in sustained remission without evidence of disease achieved stringent CR and received their IMID-dexamethasone combination at second line, suggesting that depth of response and timing increase the probability of long lasting responses. An abnormal karyotype was detected in a small percentage of patients but we had not enough results available to reach conclusions; trisomies were not observed.

Sixteen percent of patients treated with lenalidomide/dexamethasone developed solid tumors. Although, lenalidomide based regimens have been associated with cancer development in newly diagnosed patients [13] or in relapsed/ refractory MM [17], in the “exceptional responders” patients, characterized by a prolonged survival, an increased incidence of secondary malignancies could occur as in the general elderly population and be irrelevant to IMiD treatment.

In conclusion, exceptional responders do exist; further studies on their microenvironmental and genetic characteristics are extremely appealing as it could reveal some protective mechanisms. In addition, this population is candidate to be cured, especially with the addition of novel agents.

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