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Successful Early Rescue with Isatuximab Plus Carfilzomib-Dexamethasone (ISA-KD) in Daratumumab-Refractory Newly Diagnosed Multiple Myeloma (NDMM) Patients with "No Washout Period": A Real-World Clinical Experience in A Case Series and Literature Review

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Abstract

Introduction: Anti-CD38 monoclonal antibodies, such as daratumumab and isatuximab, are key agents in multiple myeloma treatment. However, sequential use without a washout period remains controversial due to resistance concerns.

Methods: We conducted a retrospective, real-world study of five newly diagnosed multiple myeloma (NDMM) patient's refractory to daratumumab-based induction. Between June 2022 and December 2024, patients from two Spanish centers received isatuximab-carfilzomib-dexamethasone (ISA-KD) immediately after daratumumab failure.

Results: All patients achieved rapid, deep responses, enabling autologous stem cell transplantation in two cases.

Conclusion: These findings suggest that immediate anti-CD38 switching may be effective. Larger studies are needed to validate this approach.

Keywords: Multiple myeloma; Monoclonal antibodies; Anti-CD38; Washout period; Rescue.

Introduction

Combinations of 3 or 4 drugs (proteasome inhibitor or PI, immunomodulatory drug or iMIDs, dexamethasone +/− anti-CD38 monoclonal antibody or mAb) have become a well-established standard for induction therapy in newly diagnosed multiple myeloma (NDMM) patients. These combinations obtain very good partial responses (VGPR) or better in >70%–90% after performing an autologous-stem-cell-transplantation (ASCT) [1, 2]. However, what should be done if a combination as daratumumab-bortezomib-lenalidomide-dexamethasone (DARA-VRD) produces a minimal or partial response?. In this scenario, the use of an isatuximab combination immediately after a daratumumab-containing regimen is nowadays not recommended by experresponse?ield [3]. Many myeloma-attending physicians might avoid the sequence of isatuximab immediately after daratumumab because of the poor clinical results reported in the literature with a second anti-CD38 mAb after failing to the first [4, 5]. Recently, we published the fast, deep and striking response achieved with isatuximab-carfilzomib-dexamethasone (ISA-KD) in a MM patient with a minimal response after 4 cycles of DARA-VRD. The ISA-KD combination was administered immediately after DARA-VRD with "no washout period" and it allowed to proceed to ASCT in a VGPR [6].

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Materials and Methods

Consecutive patients with poor initial response to a daratumumab-containing regimen, received ISA-KD as an "early rescue" with "no washout period". We are here presenting the clinical response and evolution of 5 daratumumab-refractory NDMM patients who were treated following this strategy between June 2022 and May 2025. All 5 patients received an induction therapy with a triplet or quadruplet daratumumab combination. Our aim was to analyze the response to an "early rescue" therapy with an Isatuximab-combination and with "no washout period" in these daratumumab-refractory NDMM patients. This was a descriptive, retrospective real-word experience from 2 Spanish centers. Demographic, clinical, laboratory, treatment and response data were collected.

Results

Five consecutive daratumumab-refractory NDMM patients were included in the analysis. Median age of 62 years (interquartile range [IQR] 72–54), with a predominance of the female sex. High-risk cytogenetic in 60% and median ISS-R of 2. The main clinical characteristics, therapeutic description and evolution are summarized in Table 1.

Table 1: Demographic characteristics, analytical data and rescue treatment with Isatuximab.

			Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)			54	48	72	62	75
Sex			Female	Male	Female	Male	Female
Diagnosis	**MM subtype**		IgG kappa	IgG kappa	IgA kappa	FLC kappa	FLC lambda
	Cytogenetics		t(11:14)	None	t(4;14), 1q gain	1p deL, 1q gain	17p del
	ISS, ISS-R		III, II	I, I	III, III	II, II	I, II
Analytical parameters at diagnosis	MC (g/dl)		7.36	1.99	4.13	No MC	No MC
	Serum FLC (mg/l)	K	94.67	70.36	1138.87	10341.78	3.92
		L	3.23	4.32	2.59	13.40	2088.56
1st line therapy			Dara-VRD	Dara-VRD	Dara-VCD	Dara-VTD	Dara-RD
Isatuximab	Treatment line		2ª	2ª	2ª	2ª	2ª
	Treatment scheme		Isa-KD	Isa-KD	Isa-KD	Isa-KD	Isa-KD
	Number of cycles		10	4	6	7	15
	Time since last dose of daratumumab (days)		35	35	42	5	10
Response	Response type		**VGPR**	**VGPR**	**VGPR**	**SCR**	**SCR**
	MC at the start (g/dl)		**4.68**	**1.46**	**3.73**	**0.09**	**0.19**
	FLC at the start (mg/l)	K	5.35	22.35	**1205.58**	**5570**	3.92
		L	0.64	2.18	2.27	13.7	**2644.22**
	MC last evaluation (g/dl)		**0.08**	**0.11**	**0.29**	**0**	**0**
	FLC last evaluation (mg/l)	K	2.25	1.92	**48.61**	**3.4**	0.62
		L	1.20	1.76	2.61	2.86	**23.80**

All 5 patients received an "early rescue" with ISA-KD. The median time from the last dose of daratumumab to the first of isatuximab was 35 days (IQR 35–10). All patients achieved fast and objective response to ISA-KD enabling ASCT in the two eligible patients in a VGPR status and produced a great clinical response and benefit in the other 3 patients. The biochemical response of one of the patients is graphically illustrated in Figure 1.

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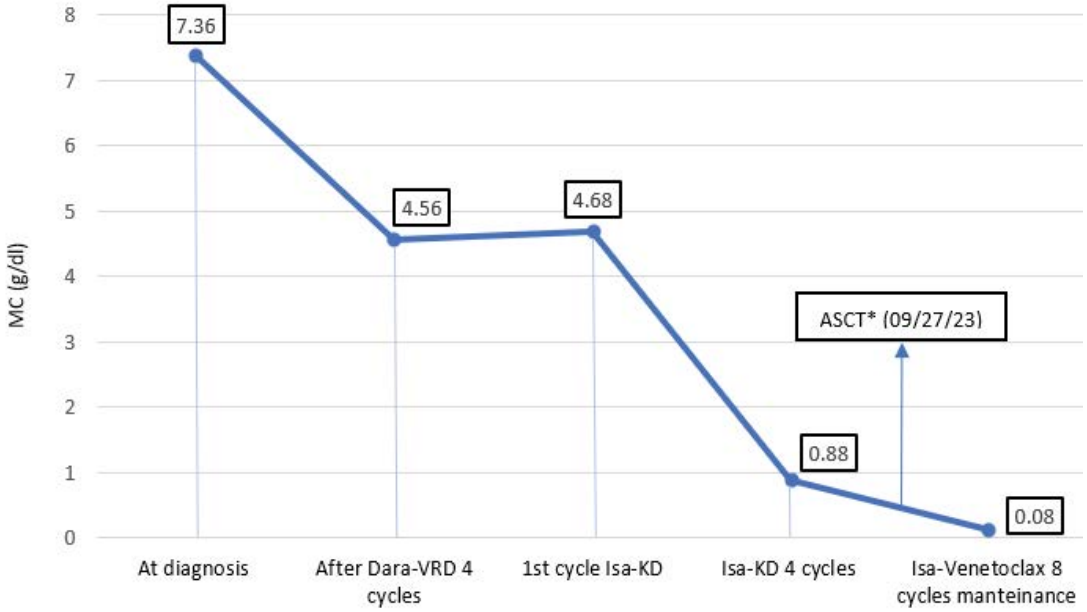

Figure 1: Case 1: biochemical evolution of serum IgG-Kappa monoclonal component.

MC: monoclonal component. ASCT: autologous stem cell transplantation. Dara-VRD: daratumumab, bortezomib, revlimid, dexamethasone. Isa-KD: isatuximab, carfilzomib, dexamethasone.

*On day +100 post-ASCT, minimal residual disease positivity was detected in the bone marrow with 0.9% plasma cells, 96% of which were identified as pathological by immunophenotyping. Maintenance therapy with isatuximab and venetoclax was initiated on 02/21/2024.

Discussion

Patients with NDMM who are non-responding or that progress after an initial quadruplet induction therapy (e.g., DARA-VRD) have a worse outcome compared to primary responders [7, 8]. In the GRIFFIN study, the large majority of NDMM responded favorably to the DARA-VRD four drugs combination (>VGPR 90% after consolidative ASCT) with only a 6.7% of disease progression under therapy [1]. Effective rescue treatments for poorly responding or primary refractory MM who failed to a quadruplet therapy are not well established. The two CD38-targeted mAb approved for use in MM are daratumumab and isatuximab. Both anti-CD38 mAb have different mechanisms of action, targeting different epitopes of the CD38 molecule at several cell lines (MM, T, and Natural Killer (NK) cells) to produce their effects on both malignant cells and immune cells of the tumoral microenvironment. Furthermore, the mechanisms of drug resistance are also different for both anti-CD38 mAb as has been extensively investigated [9]. In 2021, Mikhael J et al published the unfavorable outcomes with isatuximab monotherapy in 32 heavily pre-treated refractory/relapsing MM (RRMM) patients in a Phase 2 prospective multicenter study. These patients had received a median of seven prior lines, all had a daratumumab-refractory MM and all were also refractory to their last therapy line. A 60% of patients received a daratumumab combination just prior to isatuximab and in 62.5% of patients the interval between last daratumumab dose and first isatuximab administration was less than 6 months. As expected, the clinical outcomes were poor with an overall disease control rate (defined as more than minimal response or stable disease >8 weeks) of 37.5%. Disease control seemed to improve with a longer interval between the last daratumumab dose and the first isatuximab, giving rise to the concept of "washout period" (time without receiving an anti-CD38 mAb). Mikhael J et al observed that patients with a washout period exceeding 6 months achieved disease control in 58.3% of cases versus 28.6% for those with a washout period of less than 3 months. These poor results observed with isatuximab monotherapy after failing to daratumumab in this heavily pretreated and worse prognosis population has had a big impact on the clinical practice and the majority of hematologists are nowadays usually waiting a washout period of 3–6 months, before considering the use of isatuximab combinations in daratumumab-refractory MM [4].

Taku Kikuchi et al, reported retrospective single-centre data from a large real-world study on 39 RRMM (median of 4 prior therapy lines) who were treated with isatuximab combinations (mostly isatuximab-pomalidomide-dexamethasone (ISA-PD)) after daratumumab-containing therapies. The worst outcomes were observed in daratumumab-refractory or triple class-refractory patients, those with high lactate dehydrogenase (LDH) levels or those who received isatuximab in the 3 months after daratumumab [5]. Efstathios Kastritis et al in a one-center retrospective

analysis in heavily pretreated RRMM exposed to both anti-CD38 mAb, observed the best results when retreating with an alternative anti-CD38 mAb in those patients who attain a PFS ≥12 months with the first anti-CD38 [10]. In "ex vivo" laboratory assays termed Myeloma Drug Sensitivity Testing (My-DST) performed on 37 patients' bone marrow aspirates from 29 extensively pretreated and multirefractory MM patients, Olivia Perez de Acha et al demonstrated that MM cells from daratumumab-exposed patients regains sensitivity after >1 year, and interestingly, that in some daratumumab-refractory patients, isatuximab led to slightly better "ex vivo" results [11]. Another "In vitro" studies performed in daratumumab-refractory patients have demonstrated that CD38 mRNA is not downregulated or mutated in MM cells that maintain their surface expression of CD38 and for this reason CD38 remains a viable target in these patients. The same investigations have revealed that effector immune cells, such as CD8+ T cells and NK cells from nonresponding patients exhibit impaired functions as reduction or absence of MM cells killing capacity in an "in vitro" flow cytometry assay [12].

Different strategies to overcome daratumumab-resistance have been suggested, being one of them the use of other anti-CD38 mAb with a different mechanism of action such as isatuximab [13-15]. Isatuximab mediates a direct cytotoxicity against MM cells, in addition to the canonical Fc-dependent mechanisms of action, it induces a CD38-dependent depletion of MM cells via homotypic aggregation-associated cell death by actin cytoskeleton polymerization, caspase-dependent apoptosis, and lysosomal cell death; it also induces an allosteric modulation of CD38 that results in a higher inhibition of its ecto-enzymatic activity, and in clinical trials, isatuximab has demonstrated a great antitumoral activity alone or in combination with IMiDs or PIs [14]. PIs show substantial efficacy in combination with isatuximab, likely due to their multiple effects on MM cells and the tumor microenvironment [15].

Recently, we published the fast, deep and striking response achieved with ISA-KD in a MM patient with a minimal response after 4 cycles of DARA-VRD. The ISA-KD combination was given immediately after DARA-VRD with "no washout period" allowed us to proceed to ASCT in a VGPR status [6]. Later on, we and others have used this strategy in consecutive patients with poor initial response to an inductional daratumumab-containing regimen, administering an isatuximab-combination (ISA-KD or ISA-PD) as an "early rescue" with "no washout period". All of our 5 patients with MM refractory or poor-responding to daratumumab were treated with an efficacious Isatuximab combination (ISA-KD) very much earlier than previously described in literature (more than 4 previous lines) and they achieved objective, rapid and deep responses with no washout period between daratumumab and isatuximab. This strategy of "early switching from daratumumab to isatuximab" is of special interest in those patients who are poor-responding or refractory to an initial combination that includes daratumumab.

Conclusion

In conclusion, further real-word studies are needed in MM patients refractory to daratumumab and with few previous therapy lines, in whom combinations of Isatuximab might still be a suitable second therapy line without the need of changing the therapeutic target CD38 or expose them to newer drugs with a different mecanism of action and toxicity profile.

Contributions to the Work

Paula Gili Herreros: formal analysis, investigation, methodology, validation, writing, review and editing.

Xabier Gutiérrez López de Ocáriz: formal analysis, investigation, methodology, validation, writing, review and editing.

Patricia Garcia Ramirez: validation, writing, review and editing.

Marta Callejas Charavía: validation, writing, review and editing

Julio García-Suárez: validation, writing, review and editing.

Juan José Gil Fernández: formal analysis, investigation, methodology, validation, writing, review and editing.

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Conflict of interest statement

Juan José Gil Fernández: honoraria from Johnson&Johnson, Bristol Myers Squibb, GlaxoSmithKline, Sanofi, and Amgen. Xabier Gutiérrez López de Ocáriz: honoraria from Johnson&Johnson, AbbVie, BMS, Sanofi, GSK, Amgen, Astrazeneca, Beigene and Gilead. Paula Gili Herreros, Patricia García Ramírez, Marta Callejas Charavía and Julio García-Suárez: no relevant financial relationships to disclose.

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