Nivolumab for Treatment of Advanced Refractory High-Risk Multiple Myeloma

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INTRODUCTION

Treatment options for high-risk multiple myeloma (HRMM) are limited due refractoriness of the disease to established anti-myeloma agents. Quadruple-refractory patients are frequently observed in HRMM and represent a challenging population. Nivolumab (NIVO) is an IgG4 anti-PD-1 checkpoint inhibitors which is already FDA-approved for treatment of inoperable or metastatic melanoma, and several other highly advanced and metastasized solid and hematologic malignancies. NIVO binds to PD-1, an inhibitory signaling receptor expressed on the surface of activated T cells, and blocks the binding to and activation of PD-1 by its ligands, which results in the activation of T-cell-mediated immune responses against tumor cells. The ligands for PD-1 include programmed cell death ligand 1 (PD-L1), overexpressed on cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on APCs. Activated PD-1 negatively regulates T-cell activation and plays an essential role in tumor evasion from host immunity. In this study we analyze the impact of NIVO in highly advanced, refractory HRMM.

METHODS

We retrospectively analyzed the efficacy and clinical outcome of NIVO in 12 refractory, heavily pretreated HRMM patients who were treated in our institute between March 2015 and September 2016. NIVO was given intravenously at 3 mg/kg every 2 weeks or 3 weeks as single agent or in combination with immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), daratumumab (DARA), ipilimumab (IPI), and dexamethasone (DEX), respectively. Adverse events were documented by chart review and response rates were assessed as per IMWG criteria.

RESULTS

The median age of patients was 61.5 years (range 42 -72) with 33% females. The median time from diagnosis to NIVO treatment was 8 years. Isotypes included 3 IgG, 4 IgA, 3 light chain, 1 non-secretory, and 1 bi-clonal (IgG K + IgM L) cases. All patients had HRMM defined by UAMS GEP risk score, 5 patients had HRMM at baseline, and 7 patients developed HRMM with progression of the disease. All patients had FDG-PET active and MRI DWIBS/STIR defined bone lesions. 75% (n=9) had documented extramedullary disease defined by FDG-PET. All patients have been treated with high-dose chemotherapy and autologous stem cell transplantation (ASCT) in the past with a median of 3 ASCT (range 1 – 5). The median number of prior lines of therapy was 6 (range 2 - 13). All patients were refractory to bortezomib (BTZ) and thalidomide (THA), 92% to carfilzomib (CFZ) and lenalidomide (LEN), 67% to pomalidomide (POM), 50% to DARA. NIVO was used as single agent (n=4), in combination with IMiDs+PIs+DEX (n=2), IMiDs + DEX (n=2), IPI (n=1), IPI+IMIDs (n=1), IMiDs-PIs-DARA-DEX (n=1), and IMiDs+DARA (n=1), respectively. All patient received a dose of 3 mg/kg, except 1 patient who received 1 mg/kg. In median 2 cycles (range 1 – 9) were applied every 2 weeks (n=6) or 3 weeks (n=2).

The overall response rate (ORR) was 17%. 75% showed clinical benefit (2 PR, 2 MR, 5 SD), 25% had progressive disease. Those 2 patients who revealed PR have been on regimen consisting of NIVO+LEN+CFZ+DEX and NIVO+POM+CFZ+DARA+DEX. The 2 patients who demonstrated MR were on NIVO+POM+DEX and NIVO+LEN+CFZ+DEX. No response was seen in those patient who only received single agent NIVO. The median PFS was 5 weeks. The median overall survival was 5 months. 67% (n=8) of the patients developed adverse events which included infections (n=4, sinusitis, pericarditis, pneumonitis, colitis), general weakness (n=5), orthostatic dysregulation (n=1) and joint and bone pain (n=1).

CONCLUSIONS

NIVO can be safely applied in highly advanced, pretreated, refractory HRMM in combination with other established anti-myeloma agents. NIVO as single-agent was not effective in this heavily pretreated and immunocompromised myeloma population. NIVO in combination with IMiDs, PIs, DARA and DEX is revealing efficacy in highly pretreated and refractory HRMM. Further clinical studies are warranted in order to explore the efficacy of NIVO in combination with other anti-myeloma agents in earlier stages of HRMM, low-risk MM and non-immunocompromised patients.

[1]There are no relationships to disclose.

	Progressive disease
	Stable disease
	Partial remission or minor response

Nr.	Age	Sex	MM	Years	GEP70	ASCT	Relapses	PET	MRI	EMD	Treatment-line	BOR	CAR	IXA	THA	LEN	POM	DARA	ELO	Combination	Dose	Cycles	Response	OS (m)	PFS (w)
1	62	M	IgG K	10	LR -> HR	4	2	Y	Y	N	6	Y	Y	N	Y	Y	Y	Y	Y	CAR + LEN + DEX	3 mg/Kg	3 (2 weeks)	PR	alive	5
2	51	M	IgA K	7	LR -> HR	5	1	Y	Y	Y	13	Y	Y	N	Y	Y	N	N	N	POM + DEX	3 mg/Kg	3 (2 weeks)	MR	5	4
3	64	M	IgA K	13	LR -> HR	3	1	Y	Y	Y	12	Y	Y	N	Y	Y	Y	Y	Y	IPI	1mg/kg	2 (3 weeks)	SD	7	5
4	43	F	IgG K	0.8	HR	2	0	Y	Y	Y	4	Y	Y	N	Y	N	N	Y	N	N/A	3mg/kg	1	SD	6	3
5	57	M	IgG L	10	LR -> HR	3	2	Y	Y	N	6	Y	Y	N	Y	Y	Y	N	N	CAR + LEN + DEX	3mg/kg	2 (2 weeks)	MR	alive	4
6	72	F	L	1.2	LR -> HR	1	0	Y	Y	Y	2	Y	Y	N	Y	Y	N	N	N	N/A	3mg/kg	1	PD	2	N/A
7	42	M	IgA L	5	HR	4	1	Y	Y	Y	12	Y	Y	N	Y	Y	Y	Y	N	N/A	3mg/kg	2 (2 weeks)	SD	5	5
8	48	M	K	1	HR	2	1	Y	Y	N	2	Y	N	Y	Y	Y	N	Y	N	CAR + POM + DARA + DEX	3mg/kg	3 (3 weeks)	PR	4	4
9	72	F	K	15	HR	3	2	Y	Y	Y	5	Y	Y	N	Y	Y	Y	N	N	N/A	3mg/kg	1	PD	1	N/A
10	68	F	IgA K	9	LR -> HR	3	1	Y	Y	Y	7	Y	Y	N	Y	Y	Y	N	N	LEN + DEX	3 mg/Kg	6 (2 weeks)	SD	5	6
11	70	M	IgA K + IgM L	9	HR	4	2	Y	Y	Y	12	Y	Y	N	Y	Y	Y	N	N	IPI + POM	3 mg/Kg	9 (2 weeks)	SD	9	8
12	61	M	Non-secretory	5	LR -> HR	2	1	Y	Y	Y	3	Y	Y	N	Y	Y	Y	Y	N	DARA + POM	3 mg/Kg	1	PD	3	N/A