TIME TO DEVELOPMENT OF TREATMENT-EMERGENT PLASMACYTOMAS IN THE ERA OF NOVEL AGENTS

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Background

- The introduction of proteasome inhibitors (PI) and immunomodulatory agents (IMIDs) has had a positive impact on overall survival of patients with multiple myeloma (MM).[1]
- In the era of novel agents, concerns have been raised about an increased incidence of extramedullary disease (EMD) with the combined use of PIs and IMIDs for upfront therapy. [2,3]

Objectives

- Evaluate the time from diagnosis until development of EMD based on radiologic imaging, biopsy and/or physical examination.
- Determine whether the addition of lenalidomide (Len) to bortezomib (Bort)-based front-line regimens (e.g. RVD)[4] precipitated the more rapid development of treatment-emergent plasmacytomas.

Methods

Study Design

•We performed a retrospective chart review of 117 MM patients (pts).

Patient Population

•Pts were eligible if they enrolled in clinical trials of first-line treatment with Bort-based regimens:

- ✧with Len: Bort-Len-Dexamethasone [RVD], RVD-cyclophosphamide [Cy], RVD-vorinostat, and RVD-liposomal doxorubicin
- ✧or without Len: Bortezomib monotherapy, Melphalan-prednisone-Bort [MPV], CyBortDex, combination of MPV- CNT0328 (an anti-IL-6 antibody)

•Pts were evaluated from a protocol-derived clinical research data base at Dana-Farber Cancer Institute (DFCI) enrolling pts from December 2003 to May 2012.

Statistical Methods

•The Gray's test was reported for the comparison of time to occurrence of EMD by patient baseline characteristics in both univariate and multivariable analyses.

•Multivariable model was constructed by including all variables with p<0.15 in univariate analysis and ISS stage.

•To compare the rates of EMD, we conducted sensitivity analyses at truncated follow-up (F/U) times of 5- and 7-years, to control for any potential bias due to shorter follow-up.

Results

- Patient baseline demographics and clinical characteristics are presented in Table 1
- Overall, 69 pts received a Bort+Len regimen, while 48 pts received a Bort-without Len regimen.
  - ✧ RVD and Bort as a single agent were the most prevalent (35% and 34.2%, respectively).
- Median F/U time was 6.1 years (range 0.1- 10.2 years); 5.6 years (range 1.5-7.4) vs. 8.9 (range 0.1-10.2), respectively, for Bort+Len vs. Bort-no Len.

Table 1. Patient and Disease Characteristics at Diagnosis

Baseline Characteristics	N	(%)	Baseline Characteristics	N	(%)
Gender			IFE		
Male	73	62.4	IgG k	48	41.0
Female	44	37.6	IgG L	26	22.2
Race			IgA k	18	15.4
White	102	87.2	IgA L	8	6.8
Black	8	6.8	IgM L	1	0.9
Hispanic	4	3.4	k	7	6.0
Other	1	0.9	L	2	1.7
ISS			None	6	5.1
I	55	47.0	Plasmacytoma		
II	51	43.6	None	77	65.8
III	10	8.5	Osseous	38	32.5
Durie-Salmon (D-S)			Extraosseous	2	1.7
IA	23	19.7	Hx of MGUS		
IIA	38	32.5	No	109	93.2
IIIA	52	44.4	Yes	8	6.8
IB	1.0	0.9	Hx of SMM		
IIB	2.0	1.7	No	97	82.9
IIIB	1.0	0.9	Yes	20	17.1

- EMD was observed in the form of osseous (n= 32, 27.4%), extraosseous (n = 19, 16.2%) or any osseous or extraosseous plasmacytoma (n = 40, 34.2%) (Table 2)

Table 2. The cumulative Incidence of Plasmacytoma Progression (95% CI) for All Patients

All Patients	Osseous (%)	Extraosseous (%)	Any Plasmacytoma (%)
At 2 years	9 (4,15)	4 (2,9)	12 (7,19)
At 4 years	19 (12,26)	11(6,18)	25 (17,33)
At 5 years	23 (15,31)	15 (9,22)	30 (21,38)
At 6 years	29 (20,38)	16 (10,24)	36 (26,45)
Total Failure	32	19	40

- For the 19 pts who developed extraosseous plasmacytomas, the median OS was only 0.9 years (range 0.1-4.8 years) vs. 2.47 years (0.1-8.7) for the 32 pts with osseous plasmacytomas.
- Cytogenetic data was not associated with the development of EMD but interestingly, all pts who had extraosseous plasmacytomas did not exhibit a t(11:14) by FISH at diagnosis.
- The rates of any form of EMD showed no statistically significant difference between the 2 treatment groups (p>0.2 for all comparisons) (see Table 3).
- History of previous MGUS and low Hb (<12 g/dL) at diagnosis were associated with shorter time to development of extraosseous plasmacytomas (EOP) on univariate analyses (p= 0.06 and 0.05, respectively).
- On multivariate analysis, adjusted for ISS and other clinical risk factors, only history of MGUS retained its prognostic importance for progression of EOP.
- For progression characterized by osseous plasmacytoma, the presence of a plasmacytoma, a history of MGUS and elevated calcium (≥ 10) at diagnosis proved to be predictors of poor outcome from multivariate analysis (hazard ratio= 1.9, 2.3 and 2.6, respectively, adjusted p<0.1).

Table 3. Plasmacytoma progression-comparison between Len+ Bort and Bort-no Len with follow-up times truncated at 5 years

	T-years Progression Rate (%) (95% CI)			
	Len + Bort (N=69)	Bort-based (no Len) (N=48)	P-value	Hazard ratio
Osseous			0.663	0.84(0.38,1.84)
At 2 years	7(3,15)	11(4,21)		
At 4 years	17(9,26)	22(11,35)		
At 5 years	22(12,32)	24 (13,37)		
Total failure, N	14	11		
Extraosseous			0.204	0.53(0.20,1.41)
At 2 years	4(1,11)	4(1,13)		
At 4 years	8(3,16)	13(5,25)		
At 5 years	11(5,20)	20(10,33)		
Total failure, N	7	9		
Any Plasmacytoma			0.503	0.79(0.40,1.57)
At 2 years	10(4,19)	15(6,27)		
At 4 years	23(13,33)	26(14,39)		
At 5 years	28(17,39)	33(20, 47)		
Total failure, N	18	15		

Conclusions and Future Directions

- Based on these results, there is no evidence to suggest that combination Bort/Len-based front-line therapy (such as RVD) precipitates more rapid development of EMD.
- Long term outcome for patients with EOP in particular remains poor, supporting further studies to improve therapeutic strategies for this population in the future. [5]

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