Melanoma Brain Metastasis: Presentation, Treatment and Outcomes in the Age of Targeted- and Immuno-therapies

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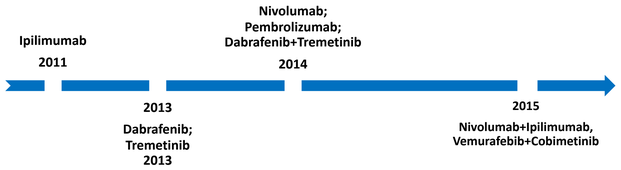
Introduction

Survival after diagnosis of melanoma brain metastasis (MBM) has historically been dismal with overall survival of 4-6 months. However, over the recent decade, numerous advances have been made in targeted therapy for melanoma, such as BRAF and MEK inhibition, as well as with immunotherapy with the approval of checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab.



These advances have resulted in significant improvements in the overall survival of patients with metastatic melanoma. Furthermore, patients with MBM have also been found to respond to these therapies. In the COMBI-MB trial, 58% of BRAF-V600E positive MBM responded to combination dabrafenib and trametinib and combination of nivolumab and ipilimumab has resulted in intracranial response in 46-56% of patients with MBM. While clinical trials have begun to include more patients with MBM, little data exists to assess how the current treatments have changed the overall prognosis of MBM diagnosis, affected CNS-directed local treatment algorithms with surgery and radiation, or enumerated factors that may inform the survival of patients with MBM. **This large retrospective, single-institution study describes the presentation, treatments, and survival of MBM patients in the contemporary immunotherapy and precision medicine era.**

Methods

This retrospective study evaluated patients treated at Memorial Sloan Kettering (MSK) between 2010-2019 with a diagnosis of cutaneous melanoma with melanoma brain metastases (MBM) and no other systemic malignancy. Kaplan-Meier methodology was used to describe overall survival (OS). Recursive partitioning analysis (RPA) and time-dependent multivariable Cox modeling were used to assess prognostic variables and associate CNS-directed treatments with OS.

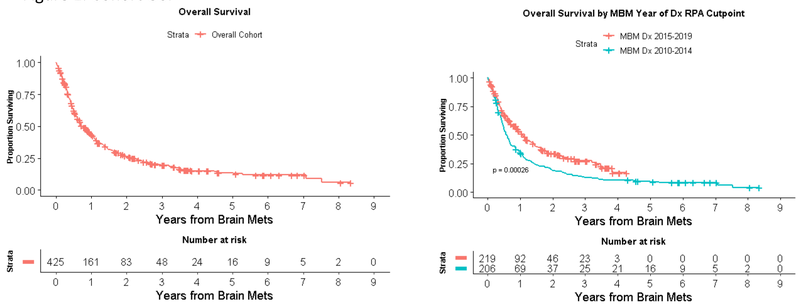
Results/Discussion

Four hundred and twenty five patients were included (Table 1). **Median OS** for the cohort was **8.9 months (95%CI: 7.9-11.3)** from MBM diagnosis (Figure 1), which compares favorably to historical cohorts reported before 2010 (median OS of 4-6 months). Recursive Partitioning Analysis (RPA) demonstrated continual improvement in prognosis and median OS based on year of MBM diagnosis: **2010-2014 (7.0 months [95%CI: 6.1-8.3]) versus 2015-2019 (13.0 months [95%CI: 10.47-17.06]); p=0.0003**. For those years, **3-year OS increased from 12.9% (95% CI: 9.0-18.6) to 27.4% (95% CI: 3.6-21.1)**, respectively.

Table 1. Patient demographics.

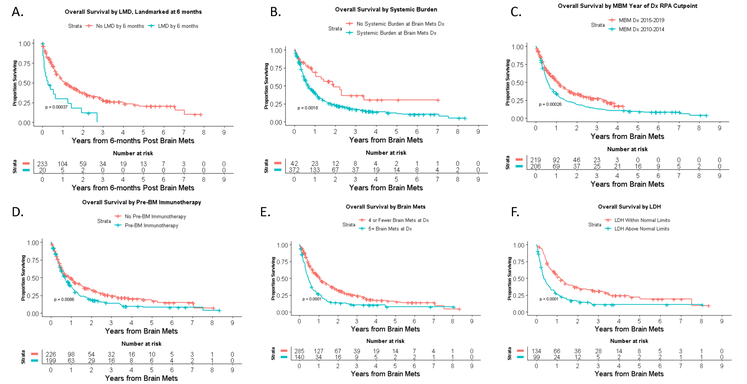
Variable	Level	N	%	Mean	Median	Min	Max
Age at MBM Diagnosis	continuous	425	100	59.3	61.3	18.9	92.4
Number of BM at Diagnosis	continuous	425	100	5.9	3	1	50
Dominant BM size (cm)	continuous	425	100	2.1	1.8	0.2	8.8
Gender	Female	121	28				
	Male	304	72				
BRAF Status	Wildtype	184	43				
	Mutated	206	49				
	Unknown	35	8				
Systemic Burden	No extracranial disease (NED)	42	10				
	Extracranial disease present	372	88				
	Unknown	11	3				
Presenting Symptom	Asymptomatic	166	39				
	Headache	72	17				
	Motor/sensory	83	20				
	Seizure	34	8				
	Mental status change	56	13				
	Other	14	3				
Hemorrhage Present in BM at Diagnosis	No	177	42				
	Yes	248	58				
Dominant BM Supratentorial/Infratentorial	Supratentorial	381	90				
	Infratentorial	44	10				
Hydrocephalus	No	382	90				
	Yes	43	10				
Cumulative Incidence of LMD @ 3 years (95% CI)	--	14.3% (95% CI:10.9-17.8)					

Figure 1. Cohort OS.



Patient overall survival (OS) significantly associated with the following (Figure 2): (A) **the presence of leptomeningeal dissemination within 6 months of diagnosis** (HR=3.90, 95%CI [2.91 - 5.23]; p= <0.0001); (B) **presence of extracranial disease** (HR=1.67, 95%CI [1.07 - 2.59]; p=0.02); (C) **2010-2014 year of MBM diagnosis** (HR=1.44, 95%CI [1.15 - 1.80]; p=0.002); (D) **administration of immunotherapy prior to the diagnosis of BM** (HR=1.41, 95%CI [1.12 - 1.76]; p=0.003); (E) **Five or more BM at diagnosis** (HR=1.79, 95%CI [1.42 - 2.26]; p= <0.0001); and (F) **serum LDH level above normal limits** (HR=2.05, 95%CI [1.52 – 2.78]; p<0.0001). Factors that were not associated with survival included age, gender, dominant BM size, presence of hemorrhage at MBM diagnosis, presenting symptom, and BRAF mutation status.

Figure 2. Prognostic factors associated with survival.



Symptomatic presentation, presence of hemorrhage, fewer BM, larger dominant BM, absence of extracranial systemic disease significantly associated with first treatment of craniotomy. SRS significantly associated with fewer BM, absence of extracranial disease, pre-MBM diagnosis immunotherapy and year of diagnosis. **With each subsequent year, the likelihood of SRS treatment increased 12% and likelihood of WBRT decreased 23%**.

Patients undergoing craniotomy had improved survival compared to those that had not (HR 0.72, 95% CI: 0.56-0.93, p = 0.01). (Table 2). Patients who underwent shunt (HR 4.24, 95% CI: 2.48-7.24, p < 0.0001) and WBRT (HR 2.65, 95% CI: 2.08-3.38, p < 0.0001) experienced shorter survival. SRS did not associate with survival on multivariable analysis.

Table 2. First treatment associates with survival.

				Univariable/Unadjusted			Multivariable/Adjusted		
Treatment	**Level**	**N**	**%**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Shunt	No	409	96	ref			ref		
	Yes (time-dependent variable)	16	4	4.14	2.45-6.99	<0.0001	4.24	2.48-7.24	<0.0001
Craniotomy	No	269	63	ref			ref		
	Yes (time-dependent variable)	156	37	0.68	0.53-0.86	0.001	0.72	0.56-0.93	0.0099
SRS	No	195	46	ref			ref		
	Yes (time-dependent variable)	230	54	0.59	0.47-0.74	<0.0001	0.87	0.68-1.13	0.3
WBRT	No	274	64	ref			ref		
	Yes (time-dependent variable)	151	36	2.96	2.37-3.69	<0.0001	2.65	2.08-3.38	<0.0001

Conclusions

This study demonstrates that the prognosis of melanoma BM has improved compared to historical cohorts and even within the later time period studied herein. The number of BM at diagnosis, systemic disease burden, and presence of leptomeningeal disease are important prognostic indicators and can guide patient counseling. As treatment paradigms continue to evolve, both CNS-directed and systemic trials should be open to and accruing melanoma BM patients in order to understand treatment efficacy on this morbid, difficult-to-treat and increasingly prevalent disease stage, and to continue improving their prognosis.