The Role of Surgical Resection of Melanoma Brain Metastases in the Immunotherapy Era

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Introduction

Immune checkpoint blockade is a treatment option for patients with melanoma brain metastases (MBM). This single institutional analysis attempted to determine the optimal management for patients with MBM undergoing craniotomy for tumor resection and immunotherapy.

Methods

An IRB approved retrospective study identified 142 MBM patients treated with immune checkpoint blockade between 2010 and 2015. Overall survival (OS) was calculated from date of diagnosis of brain metastasis until death from any cause. Model building included a prognostic model of overall survival, the effect of sequencing of immunotherapy and surgery on overall survival, and the effect of treatment sequencing on overall survival. Parallel model-building techniques were used to address the potential for guarantee-time bias.

Results

The 2-year OS for patients treated with CTLA-4, PD-1 or combinatorial blockade were 19%, 54%, and 57%, respectively. Accounting for the time-dependent covariate of surgery, factors associated with increased hazard of death included abnormal LDH, presence of extracranial disease at time of brain metastasis diagnosis, and greater than 3 brain metastases. The sequence of therapy was significantly related to survival with a 2.1-fold increase in the hazard of death when comparing patients undergoing immunotherapy +/- surgery compared to surgery + immunotherapy (HR: 2.1, 95% CI: 1.2 to 3.9, P=0.01). Patients undergoing immunotherapy prior to brain metastases diagnosis +/- surgery had a statistically significant 2.3-fold increase in the hazard of death (HR: 2.29, 95% CI: 1.2 to 4.4).

	Surgery (n=79)	No Surgery (n=63)	P
Female	27 (34.2)	21 (33.3)	0.99[a]
Age at Primary Diagnosis (Years)	55.6 ± 15.2	58.1 ± 15.1	0.40[b]
Age at CNS Metastasis Diagnosis (Years)	60.0 ± 14.5	62.0 ± 15.2	0.53[b]
Time to CNS Metastasis (Years)	4.4 ± 5.4	4.0 ± 4.3	0.75[b]
Initial Location of CNS Metastases			0.29[c]
Supratentorial	58 (73.4)	49 (77.8)	
Infratentorial	3 (3.8)	5 (7.9)	
Both	18 (22.8)	9 (14.3)	
Initial Number of CNS Metastases			0.72[c]
1	38 (48.1)	31 (49.2)	
2	14 (17.7)	9 (14.3)	
3	8 (10.1)	4 (6.4)	
More than 3	19 (24.1)	19 (30.2)	

Table 1: Prognostic model of overall survival

Predictor		Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
LDH	Abnormal vs. Normal/Missing	1.93	1.17	3.18	0.01
Presence of extracranial disease at time of CNS diagnosis	Yes vs. No	2.99	1.18	7.57	0.02
Number of CNS mets	1,2,3 vs. > 3	0.46	0.27	0.78	0.004
Synchronous CNS diagnosis	Yes vs. No	0.57	0.33	0.99	0.045
ECOG PS	2,3, or 4 vs. 0, 1	2.41	1.24	4.71	0.03
	Missing vs. 0, 1	0.84	0.43	1.64	

Table 2: Predictors of survival amongst surgical patients

Predictor		Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
WBRT	Yes vs. No	3.01	1.56	5.82	0.001
CTLA-4 blockade prior to brain metastases diagnosis	Yes vs. No	2.76	1.34	5.70	0.006
Age primary diagnosis	> 58 vs. ≤ 58 years	2.71	1.41	5.21	0.003

Table 3: Predictors of survival controlling for the time-dependent covariate of surgery

Predictor		Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
LDH	Abnormal vs. Normal/Missing	1.68	1.04	2.69	0.03
Presence of extracranial disease at time of CNS diagnosis	Yes vs. No	3.16	1.20	8.31	0.02
Number of CNS mets	1,2,3 vs. > 3	0.53	0.32	0.86	0.01
Treatment Sequence	Imm±surg vs. Surg-Im	1.97	0.99	3.93	0.04
	Im < CNS mets±Surg vs. Surg-Im *	2.29	1.20	4.36	

* *Im < CNS mets±Surg vs. Surg-Im*: Immunotherapy prior to the diagnosis of CNS metastatic disease compared to surgery prior to immunotherapy

	Surgery (n=79)	No Surgery (n=63)	P
ECOG			0.50[c]
0 (?0-1?)	31 (43.7)	26 (50.0)	
1	30 (42.3)	18 (34.6)	
2	6 (8.5)	6 (11.5)	
3-4	4 (5.6)	1 (1.9)	
4	0 (0.0)	1 (1.9)	
Radiation Therapy	74 (93.7)	49 (77.8)	0.007[a]
WBRT	25 (31.7)	17 (27.0)	0.58[a]
Immunotherapy Before Surgery (%)	48 (60.8)	N/A	N/A
Ipilimumab	67 (84.8)	54 (85.7)	0.99[a]
PD on Ipilimumab	60 (89.6)	52 (96.3)	0.30[a]
Ipilimumab/Nivolumab	5 (6.3)	3 (4.8)	0.99[a]
PD on Ipilimumab/Nivolumab	5 (100.0)	3 (100.0)	-
Anti-PD1 mAb	33 (41.8)	29 (46.0)	0.73[a]
PD on Anti-PD1 mAb	21 (61.8)	18 (62.1)	0.99[a]

Conclusions

This single institutional analysis demonstrated that the sequence of surgery and immunotherapy is associated with OS. Surgery followed by immunotherapy resulted in the longest OS for patents with newly diagnosed melanoma brain metastases, suggesting that surgical resection should be considered prior to commencing immunotherapy. A prospective, randomized trial comparing the sequence of surgery and immunotherapy for treatment naïve MBM is warranted.

Learning Objectives

-Surgery represents a critical adjunct for patients with MBM undergoing immunotherapy

-The sequencing of surgery and immunotherapy has therapeutic implications

-Upfront surgical resection of intracranial disease represents a bridge towards achieving enhanced efficacy with immunotherapy