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

Christopher Alvarez-Breckenridge; Anita Giobbie-Hurder; Corey M Gill BS, BA; Mia Bertalan BS; Naema Nayyar; Donald Lawrence; Keith T Flaherty MD; Helen Shih MD; Kevin MD Oh; Tracy Batchelor MD; Daniel P. Cahill MD; Ryan Sullivan MD; Priscilla Brastianos MD

Massachusetts General Hospital

CNS 2018 ANNUAL MEETING
HOUSTON, TEXAS
OCTOBER 6-10, 2018

Introduction

Immune checkpoint blockade provides clinical benefit for a substantial proportion of patients with metastatic melanoma; however, early intracranial metastatic progression remains a significant limitation on survival. We hypothesize that early surgical intervention creates an opportunity for improved survival amongst patients undergoing immune checkpoint blockade for metastatic melanoma.

Methods

An IRB approved, single institution retrospective study identified 142 patients with melanoma brain metastases treated with immune checkpoint blockade. Overall survival was calculated from date of diagnosis of brain metastasis until death from any cause. Model building included a prognostic model of overall survival and the effect of sequencing of immunotherapy and surgery on overall survival.

Results

A total of 79 patients underwent surgical resection of intracranial disease. The 2-year overall survival for patients treated with CTLA-4, PD-1 or combinatorial blockade were 19%, 54%, and 57%, respectively. A multivariable Cox proportional hazards model was stratified by the treatment factors of immunotherapy and surgery. Factors associated with increased hazard of death included the development of brain metastases after immunotherapy (HR: 2.05, 95% CI: 1.17 to 3.59, P=0.01), abnormal LDH (HR: 2.16, 95% CI: 1.32 to 3.54, P=0.002), and ECOG performance status greater than 1 (HR: 2.90, 95% CI: 1.55 to 5.43, P=0.004). Amongst patients undergoing surgery, a multivariable Cox

Conclusions

Amongst patients with treatment naïve melanoma brain metastases, surgical intervention represents an important therapeutic modality offering a bridge towards enhanced efficacy of immunotherapy.

Prognostic model of overall survival

Predictor		Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
1. Timing of surgery, immunotherapy and brain metastasis diagnosis	IMTX-CNS-SURG vs. CNS-SURG-IMTX	2.96	1.43	6.12	0.002
	CNS-IMTX-SURG vs. CNS-SURG-IMTX	1.31	0.53	3.28	
2. LDH	Abnormal vs. Normal/Missing	2.42	1.25	4.66	0.008
3. Age at Primary Diagnosis	≤ 58 vs. > 58 years	0.45	0.23	0.88	0.02

Predictors of overall survival amongst surgical patients

Predictor		Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
LDH	Abnormal vs. Normal/Missing	2.16	1.32	3.54	0.002
Presence of extracranial disease at time of brain metastasis diagnosis	No vs. Yes	0.32	0.12	0.80	0.02
Number of brain metastases	1,2,3 vs. > 3	0.42	0.25	0.71	0.001
Diagnosis of brain metastasis after prior immunotherapy	Yes vs. No	2.05	1.17	3.59	0.01
ECOG PS	2,3, or 4 vs. 0, 1	2.90	1.55	5.43	0.004
	Missing vs. 0, 1	1.12	0.57	2.21	

Effect of treatment sequencing with development of CNS metastasis on overall survival

Predictor		Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
LDH	Abnormal vs. Normal/Missing	1.98	1.20	3.26	0.008
Presence of extracranial disease at time of brain metastasis diagnosis	Yes vs. No	4.30	1.62	11.44	0.004
Number of brain metastasis	1,2,3 vs. > 3	0.49	0.29	0.82	0.007
Radiation	No vs. Yes (0 vs 1)	2.98	1.40	6.36	0.005
ECOG PS	2, 3, 4 vs. 0, 1	3.02	1.61	5.69	0.003
	Missing vs. 0,1	0.99	0.50	1.94	
Timing of surgery, immunotherapy and brain metastasis diagnosis	CNS-IMTX vs. CNS-SURG-IMTX	1.72	1.00	2.99	0.06
	CNS-IMTX-SURG vs. CNS-SURG-IMTX	0.75	0.30	1.91	
	IMTX-CNS-R vs. CNS-SURG-IMTX	1.87	1.004	3.48	

Findings:

Our findings demonstrate that surgery for treatment-naïve intracranial disease followed by immunotherapy is associated with increased overall survival compared to patients who a) developed brain metastases after immunotherapy, b) were solely treated with immunotherapy for brain metastases, or c) underwent surgery for brain metastases that developed on immunotherapy. These findings suggest that surgery should be considered for patients with intracranial melanoma metastases prior to the initiation of immunotherapy, particularly for those patients on corticosteroids for symptomatic disease. This aggressive surgical approach provides an opportunity to achieve unprecedented clinical benefit of emerging immunotherapies in patients previously felt to have end-stage disease.