Peri-SRS Administration of Immune Checkpoint Therapy for Melanoma Metastatic to the Brain: Investigating Efficacy and the Effects of Relative Treatment Timing on Lesion Response

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OBJECTIVE: **To investigate the efficacy of immune checkpoint therapy (ICT) administered with stereotactic radiosurgery (SRS) and determine the effects of relative treatment timing on lesion response.**

METHODS: **A prospective institutional database of all patients with intact brain metastases treated with SRS from 2008 to 2015 was reviewed for patients diagnosed with malignant melanoma. Lesion response was determined using a modified RECIST v1.1 criteria. Patients were grouped according to if they received ICT and the timing of ICT relative to SRS. Cox regression was used to identify predictors of lesion failure (LF) and distant brain failure (DBF). The Wilcoxon rank-sum test was used to compare median lesion regression after SRS between treatment groups.**

RESULTS: **Fifty-one patients with 167 metastases were evaluated. Eighteen patients (59 lesions) were treated with peri-SRS ICT with anticytotoxic T-lymphocyte-associated protein 4 or antiprogrammed cell death protein 1 therapy. Peri-SRS ICT was a significant favorable predictor for reduced hazard of LF (hazard ratio, 0.131; confidence interval, 0.028–0.610). Concurrent ICT given with SRS (hazard ratio, 0.364; confidence interval, 0.161–0.825) significantly predicted freedom from DBF. When quantitative lesion response was examined, peri-SRS ICT resulted in a significantly greater median percent lesion regression than did SRS alone at 1.5 (−30.7% vs. −14.6%; $P = 0.018$), 4 (−42.3% vs. −18.8%; $P = 0.031$), and 5 months after SRS (−52.01 vs. −14.9%; $P = 0.002$).**

CONCLUSIONS: **ICT combined with SRS was associated with greater lesion regression of melanoma brain metastases and decreased LF. When given concurrently, combined SRS and ICT may result in improved freedom from DBF.**

INTRODUCTION

Malignant melanoma has one of the fastest growing rates of incidence of any cancer type, with more than 76,000 new cases estimated in the United States during 2016.[1] Two to five percent of newly diagnosed cases present as late-stage disease with nonregional metastases.[2] The brain is a common site of metastasis and an estimated 20%–54% of deaths result from brain metastases.[2,3] The treatment of brain metastases may be increasingly important for optimizing patient outcomes, because novel agents such as immune checkpoint therapy (ICT) have shown improved control of extracranial disease.[4-6] Although melanoma has traditionally been considered to be relatively radioresistant, treatment of small intact brain metastases (IBM) from melanoma with targeted high-dose stereotactic radiosurgery (SRS) has been shown to have effective rates of lesion control.[7-11]

Key words
- Brain metastases
- Immunotherapy
- Lesion response
- Melanoma
- SRS

Abbreviations and Acronyms
Anti-CTLA 4: Anticytotoxic T-lymphocyte-associated protein 4
Anti-PD1: Antiprogrammed cell death protein 1
CI: Confidence interval
DBF: Distant brain failure
HR: Hazard ratio
IBM: Intact brain metastases
ICT: Immune checkpoint therapy
LF: Lesion failure
MR: Magnetic resonance
OS: Overall survival
RN: Radiation necrosis
SRS: Stereotactic radiosurgery
WBRT: Whole-brain radiation therapy

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Although SRS, whole-brain radiation therapy (WBRT), and surgical resection are the most commonly used treatment modalities for IBM,[12] investigations have suggested that ICT may also have therapeutic effects in the central nervous system.[13-15] Further, radiation is known to modulate both antigen presentation and the expression of immune checkpoint molecules,[16] despite previously being viewed as immunosuppressive as a result of lymphocyte toxicity,[17] which has led to interest in the potential for synergy between multimodal therapy with SRS and ICT.

Studies have investigated the effects of administering ICT in addition to SRS for treating IBM from melanoma on both survival and lesion failure (LF).[18,19] The influence of the timing of ICT administration relative to SRS on patient outcomes has been an area of active interest.[19] However, the optimal relative timing for administering ICT relative to performing SRS has not been completely defined. In our investigation, we examined patients with IBM from melanoma treated with single-fraction SRS alone and SRS with ICT. We sought to investigate if an optimal treatment interval and sequence for ICT administration relative to SRS could be found and, if found, translated to superior clinical outcomes.

METHODS

Patients

All patients with IBM from malignant melanoma treated with SRS at our institution from 2008 to 2015 were reviewed from a prospectively collected database as part of this institutional review board approved study. Lesions were excluded if they were surgically resected before SRS. The standard of practice transitioned at our center during the study interval with the U.S. Food and Drug Administration approval of ipilumumab for late-stage melanoma in 2011.[20] Patients receiving ICT during the earlier years of the study interval were more likely to receive ICT after multiple lines of previous systemic therapy secondary to sequential Food and Drug Administration approvals for ICT as second-line therapy made over the course of this study.

Treatment-naive patients with stage IV melanoma at our facility are administered ICT as first-line therapy as opposed to targeted therapy with molecular inhibitors secondary to the higher rates of durable objective response rates observed with ICT.[21-23] Patients whose histopathology demonstrate targetable mutations and have debilitating symptoms from their melanoma metastases may be considered for first-line therapy with targeted agents given their rapid onset of action.

Anticytotoxic T-lymphocyte-associated protein 4 (anti-CTLA4) or antiprogrammed cell death protein 1 (anti-PD1) ICT was considered part of the treatment regimen for IBM treated with SRS if SRS was performed within a 12-week interval of either the start or finish of ICT administration. Patients who received anti-CTLA4 therapy were treated with up to 4 doses of ipilumumab at a dose of 3 mg/kg. Patients who received anti-PD1 therapy were treated with up to 8 doses of pembrolizumab at a dose of 2 mg/kg.

Patients treated with SRS within 12 weeks of ICT administration were considered to have received peri-SRS ICT. Patients were considered to have received concurrent treatment of ICT with SRS if the first or last dose of ICT was within 4 weeks of the date SRS was performed. Patients with SRS performed within 12 weeks of ICT but outside the 4-week interval were considered to have received nonconcurrent treatment. These intervals were determined by examining time elapsed in days between first or last dose of ICT and SRS for each lesion that showed a clustering of lesions receiving SRS within 4 weeks of the first or last dose of ICT (**Online Resource 1**).

Patients with a BRAF mutation were considered to have received BRAF inhibitor therapy as part of lesion treatment if SRS was performed within 12 weeks of BRAF inhibitor therapy.

Patients were followed with gadolinium-enhanced magnetic resonance (MR) imaging after SRS. To determine lesion response, the maximal axial diameter of each lesion was measured at time of SRS and at each of the first 3 imaging follow-ups by a single reviewer to minimize the risk of interreviewer measurement variation.

Radiosurgery Technique

Ninety-two lesions were treated using the CyberKnife linear accelerator (Accuray, Sunnyvale, California, USA) and 75 lesions were treated using the Varian Trilogy linear accelerator (Varian, Palo Alto, California, USA). Patients were simulated in a supine position with a thermoplastic mask used for immobilization. MR imaging of the whole brain with 1-mm slices was fused to planning computed tomography.

Planning target volume was defined by the contrast enhancement of the lesion, incorporating targeting and setup error. No additional margin was added as part of treatment planning to minimize the risk for toxicity from an increased dose to adjacent normal brain tissue.[24] Prescription dose and isodose lines were selected at the discretion of the attending radiation oncologist, based on the safety guidelines provided by RTOG 90-05 and institutional dose-response data.[11,25] Prophylactic usage of steroids was not routine.

Statistical Analysis

Statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria). Baseline patient, lesion, and treatment characteristics were collected including diagnosis-specific graded prognostic assessment scores.[26] χ^2 tests (categorical variables) and analysis of variance (continuous variables) were used to characterize the patient cohort. Outcomes of interest included LF, freedom from distant brain failure (DBF), overall survival (OS) and percent lesion regression from time of SRS measured at the first 3 imaging follow-ups (median of 1.5, 4, and 5 months from SRS).

LF was determined using a modified response evaluation criteria in solid tumors (RECIST v1.1).[27] Lesions that required additional SRS, surgical resection with pathologic confirmation of malignancy, or showed progressive growth (>20% increase with a minimum increase of 5 mm) on MR imaging were considered LFs. In addition, lesions smaller than 1 cm had to meet the additional criterion of showing growth on a minimum of 2 consecutive imaging sequences and adhering to the other criteria.

DBF was defined by the development of new brain metastases after SRS determined by imaging, additional SRS, WBRT, or resection of a nonpreviously known tumor. OS was defined from date of SRS to death of any cause. Lesion regression was defined by percent change in greatest axial diameter from time of SRS at each of the first 3 imaging follow-ups. Neurologic death was defined by the development of new brain metastases or LF present at last imaging follow-up and not receiving subsequent therapy before death.