Acute neurologic toxicity of palliative radiotherapy for brain metastases in patients receiving immune checkpoint blockade

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Abstract

Background. The interaction between immune checkpoint blockade (ICB) and radiation (RT) for brain metastases has not been well understood. Given that acute neurotoxicity from this combination is not well characterized, we reviewed patients receiving ICB and RT for brain metastases.

Methods. Patients treated with ICB and cranial RT from 2010 through 2017 were reviewed. ICB and RT must have been administered within 30 days of each other. Treatment parameters, performance status, symptoms prior to treatment, and toxicity were extracted from the electronic medical record. Survival was calculated from the end of RT to last follow-up or death.

Results. Seventy-eight patients were included. Median follow-up was 177 days (range, 12–1603). Median age was 64 years old (range, 29–98) and 47 (63%) were male. The main tumor types were melanoma ($n = 47$) and nonsmall-cell lung cancer ($n = 19$). Fifty-seven patients were treated with stereotactic radiosurgery (SRS) and 21 with whole-brain radiotherapy (WBRT). Most patients received single-agent ICB, though 4 patients received nivolumab and ipilimumab. Forty-one (53%) patients reported no neurologic toxicity. Grade 2 or greater neurologic toxicities were reported in 12 (21%) and 8 (38%) patients in the SRS and WBRT groups, respectively. WBRT was associated with a greater risk of any neurotoxicity, though there was no correlation between ICB agent and toxicity. Sequencing of ICB and RT (ie, <30 days vs <7) did not influence rates of toxicity.

Conclusions. ICB during SRS or WBRT does not appear to worsen acute neurotoxicity compared to historical controls of RT alone.

Keywords

acute toxicity | immunotherapy | stereotactic radiosurgery | whole-brain radiotherapy

Brain metastases are estimated to occur in 25% to 47% of cancer patients.¹ Improvements in radiographic imaging have allowed for earlier detection and better characterization of metastatic lesions, and along with advancements in systemic therapy and radiotherapy (RT) techniques, improved outcomes are now being seen. There has also been a shift from whole-brain radiotherapy (WBRT) to stereotactic radiosurgery (SRS) for individuals with a limited number of brain metastases. This has been shown

to provide excellent local control while reducing the impact of RT on cognitive decline, particularly in those with a limited number of metastases and a good performance status.^{2–4} Additionally, immune checkpoint blockade (ICB) alone shows some effectiveness in patients with brain metastases^{5,6} and is rapidly changing the outlook for many patients with metastatic disease.

The combination of radiation and immunotherapy is also a growing paradigm.^{7,8} The majority of studies

relating to brain metastases have evaluated the combination of RT with ipilimumab, an ICB agent targeting cytotoxic T-lymphocyte associated protein-4 (CTLA-4),⁹⁻¹³ with some more recent studies evaluating RT combined with programmed death receptor/ligand 1 (PD-1/PD-L1).^{14,15} Trials directly comparing the efficacy of these agents to one another have not been performed, and few studies have evaluated the safety and efficacy of combined immunotherapy and WBRT.^{9,16} Furthermore, while many studies and trials to date describe treatment efficacy, only one evaluated the acute toxicity associated with this combined therapy.¹⁶ Particularly with WBRT, there is concern that neurologic toxicity from cranial RT may be accentuated by ICB given the greater volume of normal tissue irradiated. And, perhaps more important, balancing clinical benefit with any treatment-related toxicity is imperative as these combined treatments are often given near the end of life.

Therefore, given the growing use of immunotherapy in conjunction with RT in the management of brain metastases and the limited studies describing acute tolerability, we evaluated our institutional use of immunotherapy with SRS and WBRT, with a focus on acute neurologic toxicity and tolerability.

Materials and Methods

Patients treated at an academic medical institution were retrospectively evaluated under an institutional review board-approved protocol. Patients receiving palliative radiation for brain metastases from 2010 through 2017 were identified. Patients who received immune therapy within 30 days of cranial radiation were included. Concurrent therapy was defined as immune therapy and RT administered on the same day or within 7 days of each other, otherwise therapy was considered sequential. Immune therapy agents included anti-CTLA-4 (ipilimumab) and anti-PD-1/PD-L1 (atezolizumab, pembrolizumab, and nivolumab), using standard dosing. RT consisted of either SRS in 1 fraction (Gamma Knife) or 5 fractions (Linac-based SRS), or WBRT delivered by any fractionation and using conventional field arrangements with opposed lateral beams. Per institutional practice, we typically prescribe to the 50% to 80% isodose line of SRS depending on lesion size and conformity of the plan. For the whole-brain cases, 20 Gy was delivered in 5 fractions, 30 Gy in 10 fractions, and 37.5 Gy in 15 fractions, prescribed per preference of the radiation oncologist. In patients in whom multiple courses of RT and immunotherapy were administered, the first instance of combined therapy was evaluated (whether concurrent or sequential). Indication for RT was disease progression to provide improved disease control, with most patients receiving therapy between cycles of immune therapy. Any steroid use prior to treatment was limited to patients with symptoms. Steroids were not routinely prescribed, but at the discretion of the treating radiation oncologist or neurosurgeon, occasionally were given prophylactically for large treatment volumes and/or dependent on location.

All patients required a minimum of one follow-up from end of treatment, generally at 30 days, to assess delayed acute toxicity. All toxicities were recorded according to National Cancer Institute Common Terminology

Criteria for Adverse Events, version 4. Templated toxicity questionnaires completed routinely during nursing symptom assessment in our department were utilized to extract toxicity data when available, and by individually reviewing patient records.

Patient demographics, radiation treatment parameters, number of brain metastases present at time of SRS or WBRT, immune therapy agent(s) and timing of administration, and maximum toxicity during or following radiation were recorded.

Statistical analyses included Fisher exact tests and chi-squared statistics, using an $\alpha = 0.05$ and significance cutoff at $P < .05$. Median survival was evaluated as the interval from the end of RT to last follow-up or death.

Results

Patient Characteristics

A total of 293 patients were initially identified as receiving ICB and cranial RT within 6 months of each other, comprising 181 individual patients, as multiple courses of ICB and RT may have been delivered. Eighty-two patients received ICB and cranial RT within 30 days of each other, and 78 patients had sufficient follow-up to be included for analysis. Of those, 57 received SRS and 21 received WBRT. Median age was 64 (range, 29-98) and 63% were male. The most common pathologies were melanoma (60%) and nonsmall-cell lung cancer (24%). Pembrolizumab (36%), ipilimumab (32%), and nivolumab (24%) were the most common immunotherapy agents, and 2 patients (3%) received combined nivolumab and ipilimumab. The majority of patients received immune therapy sequentially (65%) rather than concurrently (35%). Three patients in the SRS group (5%) and 2 patients in the WBRT group (10%) had prior immunotherapy courses without RT. In the SRS group, 18 patients (32%) had prior CNS-directed RT before combined modality therapy and 22 patients (39%) had additional RT following combined modality therapy. In the WBRT group, 8 patients (38%) had prior CNS-directed RT before combined modality therapy and 5 patients (24%) had additional RT following combined modality therapy. A minority of patients ($n = 5$, 9%) had craniotomies prior to RT. Extracranial disease was stable in 61% of patients at the time of RT. Median survival, as measured from the end of RT, was 176 days overall: 213 days in the SRS group (range, 12-1603), and 108 days in the WBRT group (range, 15-847). Complete demographics are presented in [Table 1](#).

Stereotactic Radiosurgery Toxicity

In the 57 patients receiving SRS, 53 patients received single-fraction SRS and 4 received multifraction SRS. The median number of lesions irradiated was 3 (range, 1-20), treatment volume was 3.53 cm³ (range, 0.01-47.5), and maximum diameter was 1.7 cm (range, 0.3-8.1). Differences in the treatment parameters for single-fraction vs multifraction SRS are detailed in [Table 2](#).

At 30 days following SRS, 35 patients (61%) experienced no neurologic toxicity, 20 patients (35%) had either grade 1

Table 1 Patient Demographics

		SRS (n)	WBRT (n)	Total (n,%)
Number of patients		57	21	78
Age at time of RT, median (range)		64	64	64 (29-98)
Male sex		36	11	47 (63)
Diagnosis	Melanoma	36	11	47 (60)
	NSCLC	14	5	19 (24)
	Small cell	3	1	5 (6)
	RCC	2	2	4 (5)
	SCCA H&N	1	1	2 (3)
	Urothelial carcinoma	1	-	1 (1)
Immune therapy	Pembrolizumab	22	6	28 (36)
	Nivolumab	16	9	25 (32)
	Ipilimumab	13	6	19 (24)
	Nivolumab+ipilimumab	4	-	4 (5)
	Atezolizumab	2	-	2 (3)
Sequencing of immunotherapy/RT	Concurrent	19	8	27 (35)
	<30 days	38	13	51 (65)
	Multiple courses	3	2	5 (6)
Other brain RT	Single-fraction SRS (pre)	14	7	21 (27)
	Single-fraction SRS (post)	15	4	19 (24)
	Multifraction SRS (pre)	1	0	1 (1)
	Multifraction SRS (post)	4	1	5 (6)
	WBRT pre	3	1	4 (5)
	WBRT post	3	0	3 (4)
Extracranial disease at time of RT	Stable	35	12	47 (61)
	Progressive	21	9	30 (39)
CNS symptoms at time of RT	Yes	14	9	23 (29)
	No	43	12	55 (71)
Craniotomy prior to RT	None	49	20	69 (88)
	Within 30 days	8	1	9 (12)
Median survival post-RT (days)		213 (range, 12-1603)	108 (range, 15-845)	176

Abbreviations: CNS, central nervous system; NSCLC, nonsmall-cell lung cancer; RCC, renal cell carcinoma; RT, radiotherapy; SCCA H&N, squamous cell carcinoma of the head and neck; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

or 2 toxicity, 2 patients had grade 3 toxicity, and 1 patient had grade 5 toxicity. The most common toxicities were headache and nausea/vomiting, and the grade 3 toxicities were nausea and paresthesia/weakness. Two patients had seizures. One seizure was grade 2 and required only adjustment of antiepileptic medications that were already initiated. The second was a grade 5 seizure in a patient with no prior seizure disorder that resulted in rupture of a known aneurysm. The patient had both metastatic melanoma and male breast cancer though the CNS lesion could not be biopsied because of location. The patient did receive pembrolizumab 14 days after SRS, with the fatal seizure due to aneurysm rupture at 28 days following SRS. For the grade 3 toxicities, one had no radiographic changes on MRI while the other demonstrated disease progression.

Fifty-two patients (91%) had follow-up appointments at 2 months (60 days) or later following SRS. Of those, only 3

presented with new neurotoxicity, including grade 1 cognitive decline, grade 1 headache, and grade 2 nausea, all of which were effectively managed conservatively.

There was no clear correlation between number of prior CNS-directed RT courses, number of CNS lesions, maximum diameter, or treatment volume and the development of higher-grade acute toxicity, though numerically the median diameter and treatment volume were greatest in those experiencing grade 2 toxicities ([Supplemental Table S1](#) and [Fig. S1](#)).

Whole-Brain Radiotherapy Toxicity

Of the 21 patients receiving WBRT, 5 (25%) had fewer than 10 lesions while 16 (76%) had 10 or more lesions. Median dose and fractions were 30 Gy (range, 20-37.5) and 10

Table 2 Stereotactic Radiosurgery Treatment Details and Toxicity

		Single fraction (n = 53)	Multifraction (n = 4)	All SRS
SRS details	Number of lesions	4 (1-20)	1 (1-2)	3 (1-20)
	Max diameter (cm)	1.6 (0.3-3.7)	4.45 (3.3-8.1)	1.7 (0.3-8.1)
	Total volume (cm ³)	3.46 (0.1-26.64)	34.3 (19.07-47.5)	3.53 (0.01-47.5)
	Dose (Gy)	21 (15-21)	30 (25-30)	21 (15-30)
Neurotoxicity	None	33	2	35 (61)
	Grade 1	9	1	10 (18)
	Grade 2	9	1	10 (18)
	Grade 3	2	-	2 (4)
	Grade 5	1	-	1 (2)
Toxicity type	Headache	5	1	6 (27)
	Nausea/vomiting	5	1	6 (27)
	Ataxia	3	-	3 (14)
	Seizure	2	-	2 (9)
	Paresthesia/weakness	2	-	2 (9)
	Cognitive disturbance	1	-	1 (5)
	Dysphagia	1	-	1 (5)
	Insomnia	1	-	1 (5)
	Malaise	1	-	1 (5)

Abbreviation: SRS, stereotactic radiosurgery.

(range, 10-15), respectively. During WBRT and through 30 days following treatment, there was a distribution of patients who experienced no acute toxicity (6 patients, 29%), grade 1 toxicity (7 patients, 33%), and grade 2 toxicity (8 patients, 38%). Nine of 21 patients (43%) had neurologic symptoms at baseline prior to initiation of WBRT, 2 of whom had improved symptoms while receiving WBRT. The most common new toxicity following combined treatment was nausea (6 patients, 29%), with a variable distribution of other toxicities highlighted in [Table 3](#). There were no grade 3 or greater toxicities reported, though 3 patients were admitted to hospice shortly after WBRT because of disease progression. Toxicities were managed conservatively on an outpatient basis in all patients. Seventeen patients (81%) had follow-up appointments at 2 months (60 days) or later following WBRT. No delayed toxicities related to treatment were noted. One patient had a decline in performance status (Eastern Cooperative Oncology Group 1 to 2) due to progression of disease. Another patient was found to have 2 new metastatic lesions in the CNS but without correlative symptoms, and was treated using SRS with no noted acute toxicity or complications.

There was no correlation between the number of prior CNS-directed RT courses, number of brain lesions at time of WBRT, total dose, or fractionation with the development of acute neurotoxicity.

Immunotherapy Agent and Acute Neurotoxicity

We evaluated acute neurotoxicity by immunotherapy agent ([Supplemental Table S2](#)). In both the SRS and WBRT groups, there was no clear correlation of severity of acute toxicity and immunotherapy agent administered. Patients

Table 3 Whole-Brain Radiotherapy Treatment Details and Toxicity

Dose (Gy)	30 (range, 20-37.5)	
Fractions	10 (range, 10-15)	
<10 lesions (n, %)	5 (24)	
≥10 lesions (n, %)	16 (76)	
Neurotoxicity	None	6
	Grade 1	7
	Grade 2	8
Toxicity type	Nausea	6
	Ataxia	3
	Muscle weakness	3
	Headache	2
	Cognitive disturbance	2
	Insomnia	2
	Dysphasia	1
Dose and toxicity		
	≤30 Gy	>30 Gy
None	5	1
Grade 1	3	4
Grade 2	5	3
Number of lesions and toxicity		
	< 10 lesions	≥10 lesions
None	1	5
Grade 1	2	5
Grade 2	2	6

receiving SRS and combined nivolumab and ipilimumab did not demonstrate worse acute toxicity compared to patients receiving single agents.

Comparison of Stereotactic Radiosurgery and Whole-Brain Radiotherapy Combined with Immunotherapy

We compared the risk of acute toxicity in patient receiving SRS vs WBRT with immunotherapy. There was a significantly greater risk of developing grade 1 or greater toxicity (odds ratio 3.98, 95% confidence interval (CI) 1.34-11.79, $P = .013$); however, there was no significant difference when evaluating the risk of grade 2 or greater toxicity (odds ratio 2.31, 95% CI 0.78-6.84, $P = .13$).

Discussion

The acute neurologic toxicity experienced by patients undergoing SRS and WBRT is not well documented in the literature, and studies describing the acute toxicity of SRS and WBRT combined with immunotherapy are particularly lacking. Given that these interventions are often palliative and performed toward the end of life, we evaluated the acute toxicity experienced by patients receiving SRS or WBRT when administered alongside ICB immunotherapy. Overall, grade 2 or greater toxicity was experienced in 23% and 38% of patients receiving SRS and WBRT, respectively. In the SRS and WBRT groups, there was no correlation with the severity of toxicity and most of the factors evaluated. More patients receiving WBRT experienced acute neurologic toxicity (grade 1 or greater); however, there was no significant difference between the 2 modalities and the development of grade 2 or greater toxicity. Administration of immunotherapy concurrently (within 7 days) or sequentially (within 30 days) did not influence the frequency or severity of acute toxicity.

The available literature estimates the rate of symptomatic acute neurotoxicity following SRS at around 20% (inclusive of low to high grade). In early studies of SRS, in particular Radiation Therapy Oncology Group 90-05 (a dose-escalation study), higher-grade toxicity was more frequently observed (grades 3-5 toxicity up to 17%);¹⁷ however, those numbers have greatly improved with further understanding of size and dose limits that are now common practice in SRS. Development of grade 3 or greater toxicity is now generally well under 10%.¹⁸⁻²¹ The toxicity from the coadministration of SRS with targeted and immunotherapy is less defined; however, a recent meta-analysis by Kroeze et al showed the toxicity from combined SRS with ipilimumab appeared safe, though specific rates of acute toxicity were not provided and the data for the anti-PD-1 agents (pembrolizumab and nivolumab) were too limited to draw an overall conclusion.²² Toxicity from combined therapies, when described, has generally focused on radionecrosis or hemorrhage as markers of treatment toxicity. Studies have generally found similar rates of necrosis and hemorrhage in immunotherapy alone vs immunotherapy with SRS, but few specify the rates of symptomatic acute toxicity

experienced by the patient.²³⁻²⁷ Kiess et al retrospectively evaluated 46 patients receiving ipilimumab and single-fraction SRS, and saw acute grade 3-4 toxicity in 20% of patients.²⁴ A phase I study by Williams et al evaluated 16 patients receiving SRS or WBRT with ipilimumab, with 11 receiving SRS, and found that acute grade 1-2 neurologic toxicity was common (4 headache, 4 subclinical intracranial hemorrhage, 2 nausea/vomiting), but only 1 patient had grade 3 toxicity (headache) and no patient experienced grade 4 or 5 toxicity.²⁵ A recent larger retrospective series evaluated 260 patients receiving single or multifraction SRS and immunotherapy, and found no increase in acute toxicity with the concurrent or sequential administration of SRS and immunotherapy, and additionally suggested that combined therapy may be associated with improved local control in patients with limited CNS disease.²³ A summary of these and other relevant studies is presented in Table 4. Our results demonstrate very low rates of grade 3-5 toxicity (2 instances of grade 3 and 1 instance of grade 5), and a 23% rate of grade 2 toxicity, which is consistent with the published literature that describes toxicity from SRS alone. Thus, ICB immunotherapy with SRS does not appear to substantially increase acute neurotoxicity.

With WBRT alone, the rate of symptomatic acute neurotoxicity is ~15%-40%; however, again there are limited data describing patient-reported acute toxicity.^{28,29} A recent study by Chen et al reported grade 2-4 toxicity as high as 68%; however, this study was conducted in a population of patients >70 years old, and the rate of grade 2-4 toxicity in the SRS group was 51% for comparison.²¹ There are few studies describing the acute toxicity of immunotherapy and WBRT. In the Williams study mentioned previously, 5 patients received WBRT and immunotherapy, with 2 patients developing grade 3 neurotoxicity (hypophysitis, fatigue) and another 3 patients developing grade 1-2 toxicity (headache, hearing loss, fatigue).²⁵ Another study by Hubbeling et al reported on 29 patients receiving WBRT and immunotherapy, in which grade 3-4 adverse events occurred in 33% of patients treated concurrently (<4 weeks between immunotherapy and RT) and 6% of patients treated sequentially (>4-week separation).²⁷ A strength of their study is that they also evaluated a cohort of patients receiving WBRT without ICB immunotherapy and found similar levels of acute toxicity, suggesting that immunotherapy may not add additional toxicity over WBRT alone. Silk et al reported on 16 patients receiving WBRT and ipilimumab and found no increase in the rate or severity of toxicity compared to a matched control group receiving WBRT alone.²⁶ A summary of these and other relevant studies is presented in Table 4. In our study, the 38% rate of grade 2 toxicity is consistent with the published literature for WBRT alone, and thus the addition of immunotherapy does not appear to increase toxicity.

We did not find an association with type of immunotherapy agent and the rate or severity of toxicity when combined with SRS or WBRT. One might anticipate that the toxicity with combined ipilimumab would be greater than with atezolizumab, nivolumab, and pembrolizumab because of their baseline differences in toxicity,³⁰ and because high-grade toxicities from the newer anti-PD-1/PD-L1 agents are less frequent than those that target CTLA-4.³¹ We did not find this to be the case with

Table 4 Summary of Relevant Studies Describing Toxicity of Stereotactic Radiosurgery or Whole-Brain Radiotherapy with and without Immune Checkpoint Blockade

Study, first author (year) ^{ref}	Number of Patients	Intervention	ICB	Number of Lesions	Dose	Follow-up ^a	Toxicity (Neurologic)	Notes
Shaw (RTOG 90-05) (1996) ¹⁷	156	SRS (1 fx)	No	Single	15-24 Gy	3 years	Overall: 22% (grades 3-5); grade 3: 10%; grade 4: 10%; grade 5: 3%	
Werner-Wasik (1999) ¹⁸	78 ^b	SRS (1 or 5 fx)	No	Single	13-21 Gy	2 weeks (endpoint)	Overall: 35% (grades 1-4); grades 1-2: 87%; grade 3-4: 3%	Evaluated acute toxicity specifically within 2 weeks of RT.
Yamamoto (2014, ¹⁹ 2017) ²⁰	1194	SRS (1 fx)	No	2-15	10-25 Gy	12 months (survival post-SRS)	Overall: 12% (grades 1-4); grade 1: 4%; grade 2: 5%; grade 3: 2%; grade 4: <1%; grade 5: <1%	
Keiss (2015) ²⁴	46	SRS (1 fx)	Yes	Single	15-24 Gy	22 months	Grades 3-4: 20%	
Chen (2018) ²³	260 total 181 SRS alone 79 SRS+ICB	SRS (1 or 5 fx)	Yes	1-2	20 Gy	9.2 months	Without ICB grade 1: 32%; grade 2: 43%; grade 3: 3%; grade 4: 1%. With ICB grade 1: 19%-30%; grade 2: 35%-42%; grade 3: 3%; grade 4: none	No increased toxicity but did not specify values between the 2 groups.
Hauswald (2012) ²⁸	87	WBRT (10-20 fx)	No	Multiple	30-40 Gy	8 months	No toxicity: 81%; grades 2-3: 12%; grade 4: 7%	
Chen (2017) ²¹	119	SRS (1-5 fx) or WBRT (10-15 fx)	Yes	1-30	14-25 Gy (SRS); 30-37.5 Gy (WBRT)	3 months	WBRT grades 1-4: 89%; grades 2-4: 68%; SRS grades 1-4: 68%; grades 2-4: 51%	Much higher rates of toxicity compared to other studies, could be related to median age studied.
Williams (2017) ²⁵	16 11 SRS 5 WBRT	SRS (1 fx) or WBRT (10 fx)	Yes	1-10+	14-24 Gy (SRS); 30 Gy (WBRT)	10.5 months (SRS); 8 months (WBRT)	SRS grades 1-2: 90%; grade 3: 10% (1 patient); WBRT grades 1-2: 3 patients; grade 3: 2 patients	Common events: headache, nausea/vomiting, subclinical hemorrhage.
Hubbeling (2018) ²⁷	69 40 SRS 29 WBRT	SRS (1-5 fx) WBRT (10-15 fx)	Yes	1-21	Not specified	16 months	SRS any grade toxicity: 20%-57%; grades 3-4: 36% (<4 wks ICB/RT) vs 20-29% (>4 wks ICB/RT); WBRT any grade toxicity: 80%-88%; grades 3-4: 33% (<4 wks ICB/RT) vs 6% (>4 wks ICB/RT)	Matched control WBRT alone (no ICB); showed no increase toxicity with immune therapy compared to RT alone. Also included a small cohort of partial brain irradiation with ICB (9 patients).
Silk (2013)	70 33 SRS 37 WBRT	SRS (1-5 fx) WBRT (10-13 fx)	Yes	1-3+	14-24 Gy (SRS); 30-37.5 Gy (WBRT)		No increased toxicity with ICB, did not specify number or %	Control group didn't receive ICB both in SRS and WBRT groups. 39.4% patients in ICB group also received BRAF inhibitor therapy.
This study	78 57 SRS 21 WBRT	SRS (1-5 fx) WBRT (10-15 fx)	Yes	1-10+	14-24 Gy (SRS); 20-37.5 Gy (WBRT)	30 days	SRS grades 1-2: 35% grade; 3: 4% (2 patients); grade 5: 2% (1 patient); WBRT grade 1: 33%; grade 2: 38%	

Abbreviations: BRAF, B-Raf proto-oncogene; fx, fraction; ICB, immune checkpoint blockade; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy; wks, weeks.

^aMedian unless otherwise noted.

^bIncluded 43 nonmalignant lesions.

ipilimumab and cranial RT (WBRT or SRS); however, the use of ipilimumab and extracranial palliative RT (stereotactic body RT or larger fields) has shown some greater toxicity than when combined with the PD-1/PD-L1 agents.¹⁶

We recognize there are limitations to this study. It is retrospective in nature, and we were limited to information available during chart review. Toxicity data may be incompletely documented in the medical record as a result, and thus our data may underrepresent the toxicity experienced by patients. We also evaluated patients only up to 2 months following treatment, as our focus was on whether the acute toxicity experienced by patients was consistent with the palliative intent of these interventions; certainly later toxicities could have developed that we did not capture. Additionally, we did not compare our patients to a cohort treated with either intervention alone, though the same limitations would apply with retrospectively identifying a control cohort for comparison. Certainly the toxicities documented could result from RT or immunotherapy independent of one another. Our data are, however, consistent with the toxicity rates published in the literature for SRS or WBRT alone, and corroborate the few published studies evaluating the toxicity of immunotherapy and cranial RT (Table 4). With the expanding use of immunotherapy and improved survival in certain patients, there will likely be an associated increase in the need for palliative cranial RT (SRS or WBRT). Our findings should provide guidance to physicians offering palliative cranial RT concurrently or sequentially with immunotherapy. There is no unified definition of concurrent vs sequential therapy (ie, time between ICB and RT), nor are there guidelines specifying the appropriate amount of time, if any, to hold ICB prior to cranial radiation. While other time intervals could be evaluated, our data demonstrate acceptable toxicity rates with the administration of cranial RT within 30 days of ICB, including <7 days. These findings contribute to the limited number of studies describing acute toxicity with this combination therapy and in this particular patient population.

Conclusions

SRS and WBRT administered either concurrently or sequentially with immunotherapy appears to be safe, and results in acceptable rates of acute neurotoxicity when compared to historical controls of SRS or WBRT alone. Immunotherapy does not appear to worsen the severity of acute symptoms following CNS-directed RT. Additionally, there was no clear association between toxicity rate or severity and the type of immunotherapy agent used. Given the apparent limited differences in toxicity, patients with brain metastases who may benefit clinically from RT should still be considered for SRS or WBRT either during or following ICB.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

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