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Combining radiation therapy with systemic targeted therapies in intracranial metastatic disease

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Abstract

Approximately 20-40% of all patients with malignant neoplasms will develop intracranial metastatic disease. Importantly, due to prolonged survival with improvements in systemic therapies as well as enhanced detection with modern imaging techniques, the incidence of brain metastases is only increasing. Presently, treatment for brain metastases includes radiation therapy either with or without preceding neurosurgical intervention. Radiation therapy includes both fractionated treatment to the whole brain (WBRT) as well as high dose focused radiation directed at the metastasis itself in the form of stereotactic radiosurgery (SRS). With these techniques the rate of local control is often greater than 90%, however, the median overall survival for these patients remains poor partly due to systemic and/or distant intracranial recurrence. An exciting potential therapeutic option in this patient population is the combination of targeted therapy with radiation in an attempt to improve outcomes without significantly increasing associated toxicities. Efficacy and toxicity have yet to be fully realized in this relatively new combinatorial approach. In this article, we explore current knowledge of radiation therapy combined with targeted agents through a comprehensive review of available literature, specifically looking at the utilization of these drugs as they are combined with SRS, WBRT, or both.

Background

Metastatic disease is the most common intracranial neoplasm, occurring in 20-40% of all patients with cancer [1]. With the advent of improved imaging and prolonged survival due to advancements in systemic therapies to better control extracranial disease, the incidence of brain metastases is increasing [2]. To date, intracranial metastatic disease has been primarily treated with radiation therapy either with or without preceding neurosurgery. Historically, radiation treatment was delivered in the form of whole brain radiation therapy (WBRT), typically delivered over the course of 5-15 treatments. Over the past decade, however, there has been a significant shift away from prolonged radiation delivered to the brain to more focused, high-dose radiation treatments provided in 1-3 fractions in the form of stereotactic radiosurgery (SRS), especially in the setting of only a few metastatic lesions. SRS provides excellent local control and is well tolerated; however it inherently cannot treat preclinical metastatic disease that would have otherwise been included in a WBRT treatment [3-5].

Despite improvements in early detection, radiation treatment, and systemic therapy the prognosis of patients with brain metastases remains poor. In patients diagnosed with only a single intracranial metastatic lesion, the median overall survival following aggressive local therapy, including both WBRT and SRS, is only 6.5-8.0 months despite a local control rate of > 90% [3-7]. As there is little improvement left to gain with the already high local control rates of current radiation therapy techniques, any further improvement in progression-free and overall survivals in this patient population must come in the form of systemic treatments.

Targeted therapy, including monoclonal antibodies and molecular inhibitors either act on malignant cells directly to inhibit growth and proliferation or act upon healthy cells to enhance inherent cancer-fighting properties. Specifically, molecular inhibitors act to disrupt both intracellular pathways and extracellular receptors involved in tumor cell proliferation while immunotherapies act to either enhance tumor cell antigenicity or improve the ability of cytotoxic T-cells to recognize and destroy cancer [8,9]. These drugs have generated great excitement for improving outcomes for patients with metastatic disease. Such agents have improved penetration of the blood-brain barrier, reduce the number of tumor cells in S phase, and enhance immune mediated antitumor effects away from the irradiated lesion through a concept termed the abscopal effect [10,11]. Combining these new therapies with brain radiation must be carefully studied prior to the adoption of such practices.

In light of this guarded excitement and the need for improved outcomes in patients with intracranial metastases, many studies have been undertaken to assess for added benefit when targeted therapies are combined with radiation treatments. These studies are diverse with regard to design, tumor histology, radiation techniques, targeted therapy, sequence of treatment delivery, and endpoints assessed. Unfortunately, the outcomes of these studies have been varied as well in both outcomes and toxicity. In this review, we assess the current knowledge regarding the combination of radiation therapy with targeted agents in the setting on intracranial metastatic disease to offer improved clarity of the benefits and risks.

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Methods

A comprehensive NCBI PubMed literature search was undertaken using the AND parameter a total of three components. The first component consisted of radiation therapy techniques and included the phrases "radiation", "stereotactic", "radiosurgery", and "whole brain". The second component consisted of disease specifications and included the phrases "brain metastasis", "brain metastases", "intracranial metastasis", and "intracranial metastases". The final parameter consisted of terms associated with targeted therapies and included the phrases "targeted therapy", "immunotherapy", "BRAF inhibitor", "tyrosine kinase inhibitor", "MEK inhibitor", EGFR inhibitor", "PD-1", "PDL-1", as well as generic and brand names of clinically available targeted agents. All included studies were performed between 1990 and 2016. Using these search terms, a total of 431 published articles were returned.

Following removal of duplicated studies and review articles (358 articles removed), the remaining 73 returned articles were manually assessed by MB and CZ to ensure that they included outcomes and/or toxicities of patients treated with both targeted therapies and radiation therapy for their intracranial metastatic disease and that the study design and results were clear. Specifically, studies were only included if radiation techniques used, targeted agents utilized, respective control groups analyzed, and outcome or toxicity results were included in the respective manuscripts. In total, 31 published studies were found to meet these criteria and were included in this review.

As the focus of this manuscript is to investigate current literature for benefit and toxicity with the addition of targeted therapies to radiation therapy specifically in intracranial metastatic disease, only outcomes with regard to intracranial disease burden, intracranial toxicities, and overall survival were assessed.

Results

Non-small cell lung cancer

Of the 31 studies returned in our literature research, the most represented histology was that of non-small cell lung cancer (NSCLC) with a total of 11 papers and an additional 1 paper studying lung cancer in general (Table 1). Of these studies, 2 required SRS to be used as part of the patients' radiation therapy, 7 utilized WBRT alone, 1 required WBRT but allowed for the addition of SRS, and 2 allowed either SRS or WBRT. Targeted therapies utilized in these studies included erlotinib, crizotinib, afatinib, gefitinib, and enzataurin.

Of the employed targeted therapies in NSCLC, erlotinib has been most widely studied with inclusion in at least 7 of the reviewed manuscripts (Table 1). Interestingly, outcomes with the addition of erlotinib to brain radiation therapy have been mixed. When combined with SRS, a single study indicated a 10 month improvement in overall survival (OS) butallowed the use of two other targeted therapies as well (crizotinib and afatinib) and did not delineate numbers of patients on, or specific outcomes with, each drug individually [12]. Another study which tested NSCLC patients treated with WBRT and SRS either alone or with temozolomide or erlotinib found a progression free survival (PFS) detriment with addition of either the chemotherapeutic or targeted agent (8.6 months vs 4.6 and 4.8 months vs, respectively) with a trend towards OS detriment as well [13]. Further, this paper also indicated a significant increase in Grade 3-5 toxicities with the addition of erlotinib or temozolomide though did not address intracranial toxicity specifically. In patients treated with WBRT, the published data on the addition of erlotinib is much more favorable with 3 of the 5 respective studies indicating improvement in PFS and OS as compared to study control patients or historical controls [14-18]. Importantly, of these 5 studies which combined erlotinib with WBRT, only 1 revealed increased intracranial toxicity associated with addition of the targeted agent in the form of increased dizziness (19% *vs.* 48%) [15].

The combination of gefitinib with radiation therapy for brain metastases has been reported in 4 studies, primarily in the context of WBRT (Table 1). Of these, 2 investigated WBRT with or without gefitinib, one investigated WBRT with either temozolomide or gefitinib, and one investigated gefitinib with or without WBRT [18-21]. Of note, in the study investigating gefitinib with or without WBRT, WBRT preceded initiation of gefitinib while the therapies were concurrent in the others. Of the three studies which investigated the addition of gefitinib to WBRT, 2 demonstrated improvements in median OS and one revealed a doubling of the objective intracranial disease response rate (15.4% to 31.6%) and improvement in the intracranial disease control rate [18-20]. The study that investigated the addition of WBRT to gefitinib revealed a vast improvement in intracranial response rate with the addition of radiation therapy (9% vs. 56%) though no difference in OS was reported [21]. Importantly, no study showed increased intracranial toxicity with the combination of gefitinib to radiation therapy.

The addition of enzastaurin after WBRT for intracranial metastatic disease has been investigated by a single study and did not reveal any improvement in PFS or OS [22]. Of note, the patient population involved in this study was suboptimally defined as 'lung cancer' and not further specified, thus making its results difficult to apply (Table 1).

Lastly, the addition of tyrosine kinase inhibitors (TKIs) in general to local intracranial therapy including SRS, WBRT, and surgical resection was discussed in a comparative analysis as well [23]. This indicated that TKIs improve PFS and OS (19.8 months vs. 12.0 months and 17 months vs. 32 months, respectively) (Table 1). Incidence of intracranial toxicities was not discussed.

Renal cell carcinoma

Two studies investigated the addition of targeted agents to radiation therapy for intracranial metastases in renal cell carcinoma (RCC) [24-25]. Both studies utilized SRS alone for their respective radiation techniques. One study provided patients either sorafenib or sunitinib concurrent with SRS and revealed a median OS of 11.1 months following SRS with a local control rate of 98% [25]. Of these patients, intracranial toxicity was rare with 4% (2 patients) having post-treatment asymptomatic tumor hemorrhage and 6% (3 patients) suffering convulsions following SRS. Another study examined the addition of targeted therapy in the form of TKIs, BRAF inhibitors, or bevacizumab to SRS though did not specify the timing with which these drugs were given relative to radiation treatment [24]. This study revealed an improvement in both local control (93% vs. 60%) and OS (16.6 months vs. 7.2 months) with the addition of targeted agents when compared to matched controls who received SRS alone without any associated increase in neurotoxicity (Table 1).

Breast cancer

A total of 5 studies investigated the combination of radiation and targeted therapy in patients with breast cancer: two with SRS, two with WBRT, and one with WBRT with or without SRS or surgery [26-30]. Targeted therapies utilized in the studies trastuzumab, trastuzumab emtansine, lapatinib, and sunitinib (Table1).

Table 1. Select studies of efficacy and toxicity for combination radiotherapy and targeted agents in intracranial metastatic disease

Stereotactic Radiosurgery

Study	N	Histology	Study Design	Study Type	Radiation technique	Targeted Agent(s)	Treatment sequence	Median Follow-up	Outcomes	Intracranial Toxicity
Wang *et al.* [12]	89	NSCLC	21/25 with targetable mutations received targeted therapy	Cohort Study	SRS alone (n=41) SRS + WBRT (N=11) SRS + NSG (n=25) SRS + WBRT + NSG (n=12)	Erlotinib Crizotinib Afatinib	Not Specified	12 months	Median OS improved with use of targeted agents (21 months *vs.* 11 months)	Not discussed
Sperduto *et al.* [13]	126	NSCLC	Radiation alone *vs.* Radiation + temozolomide *vs.* Radiation + targeted agent	Randomized Controlled Trial (Phase III)	SRS + WBRT (37.5Gy/15 fractions)	Erlotinib	C	33.6 months	Median PFS worse with addition of temozolomide or erlotinib than with radiation alone (4.6 months, 4.8 months, 8.1 months) Trend toward worsened OS with addition of temozolomide or erlotinib	Worse Grdae 3-5 toxicity with addition of erlotinib or temozolomide; intracranial toxicity not specificallyaddressed
Cochran *et al.* [24]	61	RCC	Radiation alone *vs.* Radiation + targeted agent	Retrospective Analysis	SRS only	TKI mTORi Bevacizumab	Not Specified	Not Specified	Local control improved with use of targeted agent (93% *vs.* 60%) Median OS improved with use of targeted agents (16.6 months *vs.* 7.2 months)	No difference in neurotoxicty between groups
Staehler *et al.* [25]	51	RCC	Radiation + targeted agent	Prospective Study	SRS only	Sorafenib Sunitinib	C	15 months	Local control = 98% Median OS = 11.1 months	4% with asymptomatic tumor hemorrhage 6% with convulsions
Tam *et al.* [26]	57	BC	All HER2+ patients received targeted therapy	Retrospective Analysis	SRS only	Trastuzumab	C	11.0 months	6 month local control worse with trastuzumab (83.2% *vs.* 96.2%) 12 month local control worse with trastuzumab (72.4% *vs.* 85.7%) Median OS improved with trastuzumab (22 months *vs.* 12 months)	Not discussed
Carlson *et al.* [27]	7	BC	Radiation + targeted agent	Retrospective Analysis	SRS only	Trastuzumab emtansine	C	Not Specified	Not discussed	57% of patients developed Radiation Necrosis
Knisley *et al.* [33]	77	Mel.	Radiation alone *vs.* Radiation + targeted agent	Retrospective Analysis	SRS only	Ipilimumab	B/C or A	12.2 months	2 year OS improved with addition of ipilimumab (47.2% *vs.* 19.7%) Median OS improved with ipilimumab (21.3 months *vs.* 4.9 months)	No difference in neurotoxicty between groups
Mathew *et al.* [34]	58	Mel.	Radiation alone *vs.* Radiation + targeted agent	Prospective Study	SRS only	Ipilimumab	B or C or F	Not Specified	Local control not changed with addition of ipilimumab Median OS not changed with addition of ipilimumab	No difference in neurotoxicty between groups
Tazi *et al.* [35]	31	Mel.	Targeted therapy concurrent with SRS +/- targeted agent prior to SRS as well	Retrospective Analysis	SRS only	Ipilimumab	B/C *vs.* C	Not Specified	Median OS not changed between groups	No difference in neurotoxicty between groups
Kiess *et al.* [36]	46	Mel.	Radiation + targeted agent	Retrospective Analysis	SRS only	Ipilimumab	B or C or F	Not Specified	1 year intracranial regional recurrence improved with ipilimumab provided concurrent with or following SRS *vs.* before SRS (69%/64% *vs.* 92%) 1 year OS improved with ipilimumab provided concurrent with or following SRS *vs.* before SRS (65%/56% *vs.* 40%)	Numerically more likely to have headache, intralesional hemorrhage, and neurocognitive dysfunction in ipilimumab provided concurrently as opposed to before or following SRS, though numbers too small to analyze for significance

Wolf *et al.* [37]	80	Mel.	Radiation alone *vs.* Radiation + targeted agent	Prospective Study	SRS only	Dabrafenib Vemurafenib Dabrafenib/ Trametinib	B or C or F	17 months	Intracranial PFS improved with addition of BRAFi (3.9 months *vs.* 1.7 months) Median OS improved with addition of BRAFi (11.2 months *vs.* 6.7 months) Median OS improved if BRAFi provided concurrent with or following SRS (p=0.05)	No significant toxicities noted
Narayana *et al.* [31]	12	Mel.	Radiation + targeted agent	Retrospective Analysis	SRS + WBRT	Vemurafenib	C or F	12.2 months	6 month local control = 75% 6 month freedom from intracranial progression = 57% 6 month OS = 92% (Stated historical median OS = 3-5 months)	Radiation necrosis noted in single patient
Johnson *et al.* [38]	737	Various	Radiation alone *vs.* Radiation + targeted agent	Retrospective Analysis	SRS only	Not Specified	C/F or F	Not Specified	Local control trended toward improvement with the addition of targeted agents (94% vs 90%, p=0.06) 1 year OS improved with targeted agents (65% *vs.* 30%)	Not discussed
Colaco *et al.* [39]	180	Various	Radiation + targeted agent vs Radiation + chemotherapy	Retrospective Analysis	SRS only	Not Specified	B or C or F	11.7 months	Median OS improved in patients who developed Radiation Necrosis (23.7 months *vs.* 9.9 months)	Increased rate of Radiation Necrosis with use of targeted agents (32.0-37.5% *vs.* 16.9%)
Ahluwalia *et al.* [40]	14	Various	Radiation + targeted agent	Prospective Trial (Phase II)	SRS only	Sunitinib	F	Not Specified	PFS not changed compared to historical controls Median OS = 11.7 months	No significant toxicities noted
Whole Brain Radiation Therapy										
Lee *et al.* [14]	80	NSCLC	Radiation + targeted agent vs Radiation + placebo	Randomized Controlled Trial (Phase II)	WBRT only (20Gy/5 fractions)	Erlotinib	C/F	12.6 months	PFS not changed with addition of erlotinib OS not changed with addition of erlotinib	No difference in neurotoxicty between groups
Zhuang *et al.* [15]	54	NSCLC	Radiation alone *vs.* Radiation + targeted agent	Randomized Controlled Trial (Phase II)	WBRT only (30Gy/10 fractions)	Erlotinib	C	Not Specified	Local PFS improved with erlotinib (10.6 months *vs.* 6.8 months) Median OS improved with erlotinib (10.7 months *vs.* 8.9 months)	Increased dizziness with addition of erlotinib (48% *vs.* 19%)
Lind *et al.* [16]	11	NSCLC	Radiation + targeted agent	Prospective Trial (Phase I)	WBRT only (30Gy/10 fractions)	Erlotinib	C/F	95 days	Objective response rate = 64% Median PFS = 141 days Median OS = 133 days	No significant toxicities noted
Welsh *et al.* [17]	40	NSCLC	Radiation + targeted agent	Prospective Trial (Phase II)	WBRT only (30-35Gy/10-14 fractions)	Erlotinib	C/F	28.5 months	Intracranial response rate = 86% Median PFS = 8 months Median OS = 11.8 months Median OS in patients known to be EGFR mutant = 19.1 months	No increase in neurotoxicty above expected levels
Fan *et al.* [18]	186	NSCLC	Radiation alone vs Radiation + targeted agent vs Radiation + chemotherapy	Retrospective Analysis	WBRT +/- SRS +/- NSG	Gefitinib Erlotinib	C	12.5 months	Median OS improved with addition of targeted agent versus chemotherapy (12 months *vs.* 9 months)	Not discussed
Pesce *et al.* [20]	59	NSCLC	Radiation + targeted agent *vs.* Radiation + temozolomide	Randomized Controlled Trial (Phase II)	WBRT only (30Gy/10 fractions)	Gefitinib	C	34 months	Median OS improved with gefitinib (6.3 months *vs.* 4.9 months)	No difference in neurotoxicty between groups
Ceresoli *et al.* [21]	41	NSCLC	Targeted therapy +/- WBRT	Prospective Study	WBRT only	Gefitinib	F	Not Specified	Response rate improved with addition of WBRT (56% *vs.* 9%)	No significant toxicities noted

Gronberg *et al.* [22]	109	Lung Cancer (NOS)	Radiation + targeted agent vs Radiation + placebo	Randomized Controlled Trial (Phase II)	WBRT only (20-30Gy/5-10 fractions)	Enzastaurin	F	9 months	PFS not changed between groups OS not changed between groups	No difference in neurotoxicty between groups
Le Scodan *et al.* [28]	130	BC	Radiation alone *vs.* Radiation + targeted agent	Prospective Study	WBRT (30Gy/10 fractions) +/- SRS +/- NSG	Trastuzumab	Not Specified	6.3 months	Median OS improved with trastuzumab (19.5 months *vs.* 5.6 months) 1 year OS improved with trastuzumab (62.6% *vs.* 29.2%)	Not discussed
Lin *et al.* [29]	35	BC (HER2+)	Radiation + targeted agent	Prospective Trial (Phase I)	WBRT only (37.5Gy/15 fractions)	Lapatinib	C/F	6 months	Intracranial response rate = 79% 8 month PFS = 46%	14% with memory impairment 1 patient had post-treatment seizure
Niravath *et al.* [30]	12	BC	Radiation + targeted agent	Prospective Trial (Phase Ii)	WBRT only	Sunitinib	F	Not Specified	PFS not changed compared to historical controls	No significant toxicities noted
Lao *et al.* [42]	24	Various	Radiation + targeted agent	Prospective Trial (Phase I)	WBRT only (30-37.5Gy/10-15 fractions)	Bortezomib	C	Not Specified	Objective response rate = 71% Median OS = 5 months	Significant increase in radial diffusivity of the hippocampus, thought to predict future cognitive impairment
Wuthrick *et al.* [41]	12	Various	Radiation + targeted agent	Prospective Trial (Phase Ib)	WBRT or partial brain radiation therapy	Sunitinib	C	34.2 months	Objective response rate = 80% 6 month PFS = 67% Median OS = 7.6 months	No significant toxicities noted
Stereotactic Radiosurgery or Whole brain Radiation Therapy										
Fu *et al.* [19]	161	NSCLC	Radiation alone *vs.* Radiation + targeted agent	Retrospective Analysis	SRS or WBRT	Gefitinib	C	12 weeks	Objective response rate improved with gefitinib (31.6% *vs.* 15.4% Disease control rate improved with gefitinib (78.9% *vs.* 60.2%)	No difference in neurotoxicty between groups
Cai *et al.* [23]	282	NSCLC	Radiation alone *vs.* Radiation + targeted agent	Retrospective Analysis	SRS or WBRT or NSG	TKI (NOS)	Not Specified	28 months	Intracranial PFS improved with addition of TKI (19.8 months *vs.* 12.0 months) Median OS improved with addition of TKI (32months *vs.* 17 months)	Not discussed
Silk *et al.* [32]	70	Mel.	Radiation alone *vs.* Radiation + targeted agent	Retrospective Analysis	SRS or WBRT	Ipilimumab	B or F	Not Specified	Median OS improved with ipilimumab (18.3 months *vs.* 5.3 months) Median OS not improved with ipilimumab if patient received WBRT (3.1 months *vs.* 5.3 months) Median OS better if ipilimumab provided following radiation therapy than before (18.4 months *vs.* 8.1 months)	No difference in neurotoxicty between groups

In the two studies exploring the use of targeted therapies in combination with SRS, the results were generally unfavorable. One of the studies provided trastuzumab concurrently with SRS for all patients who were HER-2 positive and compared their outcomes with HER-2 negative patients who were provided SRS alone [26]. Interestingly, local control at both 6 and 12 months following SRS were found to be worse with the addition of trastuzumab (83.2% vs. 96.2% and 72.4% vs. 85.7%, respectively) though median OS was improved (22 months vs. 12 months). No information regarding intracranial toxicity was discussed in this publication. A second study provided trastuzumab emtansine, which incorporates the HER2 targeted actions of trastuzumab with the microtubule inhibitor DM1, concurrent with SRS to seven patients. While no information regarding outcomes was provided in the study, four patients developed radiation necrosis [27].

The combination of targeted agents with WBRT in breast cancer provided more heterogeneous results (Table 1). One study explored the combination of trastuzumab with WBRT as compared to patients receiving WBRT alone, though did not specify the sequence with which the interventions were provided in the study group [28]. Importantly, patients enrolled in this study were allowed to have SRS or surgical intervention in addition to WBRT. Both median OS (19.5 months vs. 5.6 months) and OS at 1 year (63.6% vs. 29.2%) were found to be improved with addition of trastuzumab though any associated toxicity with this combination was not revealed. A second single-arm study provided lapatinib both concurrent with and following WBRT to HER-

2 positive patients [29]. In this study, intracranial response rate was 79% with an 8 month PFS of 46%. Following this combination, 14% of patients were noted to have memory impairment and a single patient had post treatment seizure activity. A third study analyzed patients who were provided sunitinib following WBRT and noted no improvement in PFS compared to historical controls though additionally noted no significant treatment associated intracranial toxicities [30].

Melanoma

Data regarding the combination of targeted therapy with radiation treatments for brain metastases from melanoma are primarily derived from studies utilizing SRS alone (Table 1). Of the 7 such studies, only two included WBRT, one which utilized it in combination with SRS and one which allowed patients to be treated with either SRS or WBRT [31-32].

Of the five studies that utilized SRS as the only radiation modality, four specifically studied it with ipilimumab while the fifth examined SRS in combination with BRAF inhibitors including dabrafenib, vemurafenib, and the combination of dabrafenib/trametinib (Table 1). Two studies compared the combination of ipilimumab with SRS to SRS alone. One demonstrated improved median and 2 year OS (21.3 months vs. 4.9 months and 47.2% vs. 19.7%, respectively) while the other study showed that both local control and median OS did not differ between the groups [33-34]. Neither study revealed any increase in neurotoxicity with this combination. Another study specifically investigated timing of ipilimumab relative to SRS by comparing patients treated with ipilimumab both prior to and concurrent with SRS to those started on ipilimumab at the same time SRS was provided. This revealed no difference in median OS or neurotoxicity between these groups [35]. A second study attempted to provide insight regarding the importance of therapeutic sequence when combining SRS and ipilumumab [36]. Interestingly, patients provided ipilimumab either concurrent with or following SRS had a significant improvement in intracranial regional recurrence at 1 year and 1-year OS when compared to those who received ipilimumab before SRS only (69%/64% vs. 92% and 65%/56% vs. 40%). Numerically, patients who received concurrent treatment were more likely to suffer from posttreatment headache, intralesional hemorrhage, and neurocognitive dysfunction when compared to those who received the immunotherapy only sequentially, although this was not statistically significant, likely due to small sample size. The sole study examining the combination of BRAF inhibitors with SRS revealed that addition of these targeted agents improved intracranial PFS (3.9 months vs. 1.7 months) and median OS (11.2 months vs. 6.7 months) when compared to control patients who received SRS alone [37]. While this study did not specify sequence of treatment with BRAF inhibitors with regard to SRS, subgroup analysis revealed that median OS for those treated with BRAF inhibitor concurrently with or following SRS was superior to that of patients placed on a BRAF inhibitor prior to radiation treatment (P=0.05)

Both studies utilizing WBRT in combination with targeted agents for intracranial melanoma metastases revealed promising results (Table 1). A small study of patients receiving vemurafenib either concurrent with or following both SRS and WBRT demonstrated a 6-month local control rate of 75%, with 57% remainingfree from other sites of intracranial progression at the same time point [31]. Additionally, this combination led to a 6-month OS of 92%, much improved from the historical median OS of three to five months, and without any significant neurotoxicity. The second study included patients treated with either SRS or WBRT with or without the addition of ipilimumab [32]. Interestingly, the combination of sequential ipilimumab and radiation therapy improved median OS when patients were treated with SRS (18.3 months vs. 5.3 months) but not WBRT (3.1 months vs. 5.3 months). To clarify, ipilimumab was not given concurrent with radiation in this study and patients who received the targeted agent following_but not preceding radiation had an improved median OS (18.4 months vs. 8.1 months).

General oncology

Though difficult to extrapolate to individual patient scenarios, five studies examined the use of targeted therapy in combination with radiation for unselected intracranial metastases (Table 1). Of these, two studies examined the addition of nonspecified targeted agents to SRS with respective control groups of SRS alone and SRS combined with traditional systemic chemotherapy [38-39]. In a retrospective review, the addition of targeted agents to SRS alone improved one-year OS (65% vs. 30%) with a trend towards improvement in local control as well (94% vs. 90%, p=0.06) [38]. Retrospectively comparing to SRS with traditional chemotherapy, however, the addition of targeted therapy particularly immune therapy to SRS significantly increased the rate of radiation necrosis (37.5% vs. 16.9%) though those who developed radiation necrosis had significant improvement in median OS compared to those who did not (23.7 months vs. 9.9 months) [39]. Another study included only patients treated with sunitinib following SRS and revealed that neither PFS nor median OS were significantly different from those of historical controls [40]. When sunitinib was combined concurrently with WBRT, however, 6 month PFS and median OS of 67% and 7.6 months, respectively, were shown [41]. Lastly, the combination of bortezomib concurrent with WBRT has also been examined and revealed an objective response rate (71%) and median OS (5 months) similar to that which would be expected from WBRT alone with an associated significant increase in radial diffusivity of the hippocampus, thought to predict future cognitive impairment, on follow-up imaging [42].

Discussion

General interpretation of the benefits of targeted therapy combined with radiation treatment for intracranial metastatic disease is unsurprisingly difficult due to the significant heterogeneity of tumor biology, variable actions of targeted agents, differences in sequences of therapy, and paucity of prospective and placebo-controlled clinical trials. Reviewing all currently published data, it appears that the addition of targeted agents to radiation therapy for brain metastases is often beneficial as shown in 18 of the 31 studies discussed in this review with only a minority of studies indicating that it may lead to increased harm.

Tyrosine kinase inhibitors are the most widely studied class of targeted agents in combination with radiation therapy for brain metastases. The majority of studies support improvement in median OS with local control and PFS improved in several studies as well. Importantly, these benefits appear to be present regardless of the radiation modality utilized. A single study did indicate that the combination of TKIs, particularly erlotinib, with SRS and WBRT together was actually associated with worse outcomes and increased toxicity, though importantly all associated toxicities revealed in this study were extracranial in nature and therefore unlikely to be due to the therapeutic combination but rather the erlotinib itself [13].

Evidence regarding the addition of immunotherapy to brain irradiation for intracranial metastases is limited, consisting solely of

studies using ipilimumab in patients with metastatic melanoma. In these patients, this immunotherapeutic was not found to significantly increase intracranial toxicity with one study indicating that its addition resulted in improvement in overall survival [33]. Additionally, a study by Kiess, et al. further indicated that intracranial recurrence and overall survival at 1 year is improved if ipilimumab is provided concurrent with or following SRS as opposed to before initiation of the radiation treatment, suggesting that either the addition of immunotherapy after initiation of SRS is beneficial or its addition prior to brain radiation is somehow detrimental [36].

Interestingly, outcomes associated with the addition of trastuzumab to radiation treatment for brain metastases from breast cancer may be dependent on radiation technique utilized. When combined with SRS, current evidence suggests that trastuzumab is harmful, leading to decreased local control as well as significantly increasing the risk of radiation necrosis beyond what would be otherwise expected [26-27]. Interestingly however, median OS is noted to be improved in this group, likely due to the efficacy of trastuzumab on extracranial disease and potentiating that the reported worsened local control with the combination therapy may in fact be due to pseudoprogression as opposed to true local failure. When combined with WBRT, both median and 1 year overall survivals are again improved with the addition of trastuzumab though no information is available regarding local control or intracranial PFS with this combination [28]. Interpretation of this latter study is further hindered, however, due to the fact that both neurosurgical intervention and SRS were allowed in addition to WBRT though no analysis was provided to discuss if these combinations altered the overall results.

Importantly, intracranial toxicity associated with the addition of targeted agents to cranial radiation therapy for metastatic disease appears generally mild. Only two studies indicated an increase in associated radiation necrosis with the use of targeted agents, one with trastuzumab emtansine and another which did not specify type of targeted therapy used, in combination with SRS [27,39]. A single study noted a numeric increase in neurocognitive dysfunction with the addition of ipilimumab to SRS though was unable to assess this for statistical significance due to generally low incidence while another revealed increased hippocampal radial diffusivity following

Table 2. Select current clinical trials exploring targeted agents in combination with radiation therapy for intracranial metastatic disease

ID	*Phase*	*Status*	*Histology*	*Radiation Technique*	*Drug*	*Target*	*Study Arms*
NCT01926171	IV	Recruiting	NSCLC	WBRT	Icotinib	EGFR	1) WBRT + Icotinib
NCT01887795	III	Completed	NSCLC	WBRT	Erlotinib	EGFR	1) WBRT + Erlotinib 2) WBRT
NCT02714010	III	Recruiting	NSCLC	WBRT	Erlotinib Gefitinib Icotinib	EGFR	1) WBRT + TKI 2) TKI
NCT2338011	II/III	Recruiting	NSCLC	WBRT	Gefitinib	EGFR	1) WBRT+ Gefitinib 2) Gefitinib
NCT01514877	II	Completed	NSCLC	WBRT	Icotinib	EGFR	1) WBRT + Icotinib
NCT02662725	II	Completed	Melanoma	SRS	Ipilimumab	CTLA-4	1) SRS + Ipilimumab
NCT00871923	II	Accrual Complete	NSCLC	WBRT	Erlotinib	EGFR	1) WBRT + Erlotinib
NCT00263588	II	Accrual Complete	Breast (HER2+), progressing following radiation therapy	WBRT or SRS	Lapatinib	EGFR and HER2	1) WBRT or SRS + Lapatinib
NCT01721603	II	Accrual Complete	Melanoma	SRS	Dabrafenib	BRAF	1) SRS + Dabrafenib
NCT02556593	II	Enrolling, invitation only	NSCLC	IMRT	Erlotinib	EGFR	1) Radiation + Erlotinib 1) Radiation
NCT02726568	II	Recruiting	NSCLC	WBRT	Icotinib	EGFR	1) Iconitib until progression, then WBRT
NCT01518621	II	Recruiting	NSCLC	WBRT	Erlotinib	EGFR	1) WBRT + Erlotinib 2) WBRT
NCT02882984	II	Recruiting	NSCLC	WBRT or Hypofractionated WBRT	Erlotinib Gefitinib Icotinib	EGFR	1) WBRT + TKI 2) Hypofractionated WBRT + TKI
NCT01763385	II	Recruiting	NSCLC	Not Specified	Erlotinib	EGFR	1) Radiation + Erlotinib 2) Secondary radiation + Erlotinib
NCT01622868	II	Recruiting	Breast (HER2+)	WBRT or SRS	Lapatinib	EGFR and HER2	1) WBRT or SRS + Lepatinib 2) WBRT or SRS
NCT02097732	II	Recruiting	Melanoma	SRS	Ipilimumab	CTLA-4	1) SRS + Ipilimumab
NCT01898130	II	Recruiting	Various, progressing following radiation therapy	WBRT	Bevacizumab	VEGF	1) WBRT + bevacizumab
NCT02768337	I/II	Recruiting	Lung and Breast	SRS (low dose)	Afatinib	EGFR and HER2	1) NSG + Afatinib 2) NSG + Afatinib + 2Gy SRS 3) NSG + Afatinib + 4Gy SRS
NCT01703507	I	Accrual Complete	Melanoma	WBRT or SRS	Ipilimumab	CTLA-4	1) WBRT + Ipilimumab 2) SRS + Ipilimumab
NCT01276210	I	Accrual Complete	Various	SRS	Sorafenib	Tyrosine Kinase	1) SRS + Sorafenib
NCT02107755	I	Recruiting	Melanoma	SRS	Ipilimumab	CTLA-4	1) SRS + Ipilimumab
NCT02716948	I	Recruiting	Melanoma	SRS	Nivolumab	PD-1	1) SRS + Nivolumab
NCT01724606	I	Recruiting	Breast	WBRT	Sorafenib	Tyrosine Kinase	1) WBRT + Sorafenib
NCT02672995	I	Recruiting	Various	SRS	Bevacizumab	VEGF	1) SRS + Bevacizumab 2) Fractionated SRS + Bevacizumab

WBRT combined with bortezomib, an imaging finding thought to represent likelihood of future cognitive impairment [36,42-43]. Other toxicities noted in singular studies included increased headache and asymptomatic intralesional hemorrhage when ipilimumab was added to SRS and increased dizziness from the addition of erlotinib to WBRT [36,15]. Additionally, multiple studies indicated that their respective targeted agents combined with either SRS or WBRT did not provide significant intracranial benefit or improved survival but also did not significantly increase toxicity (Table 1). While these reports do not provide evidence to add targeted therapies to standard radiation techniques for brain lesions specifically, they do suggest that the combination is not detrimental and need not be avoided, especially in patients with extracranial disease burden that these targeted agents may help to address.

Another interesting and potentially important point with regards to the combination of targeted agents with cranial radiation therapy is the timing with which the interventions should be provided. Unfortunately, little information is currently available in this regard. As discussed above, the utilization of ipilimumab either concurrent with or following SRS provided significantly better outcomes than if provided before SRS, although concurrent treatment was noted to increase toxicity including headache, tumor hemorrhage, and neurocognitive dysfunction [36]. Similarly, a study utilizing ipilimumab either before or after either WBRT or SRS demonstrated better OS if ipilimumab was provided after SRS than before [32]. Another study, also looking and the addition of ipilimumab to SRS noted that there was no difference in outcome or toxicity if the immunotherapeutic was provided both before and concurrent with SRS as opposed to concurrent only [35]. While in total these results do not provide a clear picture of how sequencing therapy changes outcome or toxicity when targeted agents and radiation treatment are combined, they do indicate that it may in fact be an important consideration. To date, no study has attempted to address this question outside of the realm of immunotherapy and review of the current literature does not provide any obvious inferences.

In light of the lack of prospective controlled studies exploring the combination of radiation therapy with targeted agents in patients with intracranial metastatic disease as well as the heterogeneity of the available data, there remains significant need for future study. Specifically, prospective studies must be designed to limit confounding variables and provide ample power for interpretation to better delineate the true efficacy and toxicity of these therapeutic combinations. Though included in a number of the current studies, particular focus must be placed on molecular characteristics of patient tumors in future studies as well to maximize benefit and better interpret their results. More comprehensive investigation into intracranial toxicity is also required as many current studies either combine intracranial and extracranial toxicities, precluding interpretation of the added toxicity of the two interventions together beyond the toxicities associated with the targeted agent alone, or ignore intracranial toxicity altogether. Additionally, further study is warranted into how the sequence of treatment with targeted agents relative to radiation therapy alters efficacy and toxicity. With the general positivity of current data as described above, we anxiously await results from ongoing clinical trials (Table 2) in the hopes that they will provide improved insight into this exciting realm of current and future cancer therapy.

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