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REVIEW

Combined irradiation and targeted therapy or immune checkpoint blockade in brain metastases: toxicities and efficacy

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Background: Targeted therapies (TT) and immune checkpoint inhibitors (ICI) are currently modifying the landscape of metastatic cancer management and are increasingly used over the course of many cancers treatment. They allow long-term survival with controlled extra-cerebral disease, contributing to the increasing incidence of brain metastases (BMs). Radiation therapy remains the cornerstone of BMs treatment (either whole brain irradiation or stereotactic radiosurgery), and investigating the safety profile of radiation therapy combined with TT or ICI is of high interest. Discontinuing an efficient systemic therapy, when BMs irradiation is considered, might allow systemic disease progression and, on the other hand, the mechanisms of action of these two therapeutic modalities might lead to unexpected toxicities and/or greater efficacy, when combined.

Patients and methods: We carried out a systematic literature review focusing on the safety profile and the efficacy of BMs radiation therapy combined with targeted agents or ICI, emphasizing on the role (if any) of the sequence of combination scheme (drug given before, during, and/or after radiation therapy).

Results: Whereas no relevant toxicity has been noticed with most of these drugs, the concomitant use of some other drugs with brain irradiation requires caution.

Conclusion: Most of available studies appear to advocate for TT or ICI combination with radiation therapy, without altering the clinical safety profiles, allowing the maintenance of systemic treatments when stereotactic radiation therapy is considered. Cognitive functions, health-related quality of life and radiation necrosis risk remain to be assessed. The results of prospective studies are awaited in order to complete and validate the above discussed retrospective data.

Key words: cerebral, radiation therapy, immunotherapy, combination, toxicity, radiosurgery

Introduction

Brain metastases (BMs) management has evolved from whole-brain radiotherapy (WBRT) as a 'one-size-fits-all' policy to tailored treatments, in the context of new systemic agents, participating in brain control. Treatment options include surgery, stereotactic radiosurgery (SRS), WBRT, and systemic agents, alone or combined. Due to WBRT-induced neurotoxicity, stereotactic radiosurgery is increasingly considered in BMs management, even in multiple BMs setting, provided the disease burden is limited [1]. WBRT still remains the gold standard in patients with a large burden of symptomatic disease. When asymptomatic and not functional-threatening, multiple BMs might be treated with systemic agents active on primary disease, postponing SRS or WBRT.

Tumor cells response to ionizing radiations involves the activation of various cellular signal transduction pathways, altering DNA-repair and cell-growth genes expression, some of them paradoxically promoting pro-oncogenes. Targeting the RT-activated signaling pathways promoting cell-proliferation, and thus radio-resistance, might enhance RT efficacy.

Moreover, RT has long been recognized as an immune-modulator, more recently known to promote cancer cell phenotype

changes, potentially making them better targets for immune cells reactivity [2]. The limited rate of solid tumor patients responding to immune checkpoint inhibitors (ICI) prompts for new investigations, especially for the use of combined therapies such as RT, in an attempt to enhance ICI efficacy.

We herein propose to overview the combination of RT and targeted therapies (TT) or ICI in patients with BM, focusing on its safety and efficacy. The sequence of treatment delivery will also be part of the discussion. Importantly, it must be noticed that the cumulative rate of RT adverse events, including radiation necrosis (RN) is directly linked to the median follow-up of surviving patients, rising with time with no plateau [3].

Literature review search

We carried out a literature review search, using Medline PubMed and Web of sciences databases from 2000 to 2017 (March), focusing on studies investigating the safety and efficacy of TT or ICI associated with brain RT for BM. We identified and reviewed relevant clinical trials report in the international literature, and the reference list from these sources was manually searched for additional relevant trials. Review articles were not included. Data extracted from these studies included: number of patients evaluated in the combined treatment arm of the study, type of RT, administration sequence, mutation status if any, duration of the follow-up, disease control rate, median survival, overall survival (OS), and toxicities. RT was considered administered 'concurrently' with systemic therapy when administered in a period less than five half-lives of the drug (Table 1). Data extracted from text, tables and figures of the articles were then tabulated.

Table 1. Drugs half-lives (approximate values, from transparency commissions)

Drug	Median half-life (h)
Vemurafenib	51.6 (29.8–119.5)
Dabrafenid	8 (when orally administered)
Trametinib	127
Erlotinib	36.2
Gefitinib	41
Sunitinib	95
Bevacizumab	480
Trastuzumab	456
Lapatinib	24
Trastuzumab-emtansine	96
Ipilimumab	370
Pembrozilumab	600
Nivolumab	578

Radiotherapy and targeted therapy

BRAF inhibitors

The mitogen-activated protein kinase (MAPK) pathway, activated after ionizing radiation exposure, leads to cell proliferation, survival, and differentiation. Reversing this paradoxical ionizing radiation-effect, through MAPK signaling pathway inhibition, was successfully tested in pre-clinical models, leading to tumor cells radio-sensitivity enhancement [4, 5].

Some case reports suggested unexpected toxicities in the portal field area, when combining RT and BRAF inhibitors (BRAF-I) [6–13].

WBRT and BRAF-I. In six out of eight studies or case reports [7–9, 11, 13–16] examining the tolerance of WBRT combined with BRAF-I, patients were given BRAF-I *before and during WBRT* [7–9, 11, 13, 16]. Four case reports warned against severe skin side-effects, despite partial response or stable disease [7, 9, 11, 13]. Severe skin-toxicity was mainly limited to the irradiated area, and resembled cutis vercitis gyrate. It occurred a few weeks after WBRT completion, and in most cases ceased up under symptomatic therapeutic, Vemurafenib being maintained without toxicity recurrence. One study retrospectively compared 123 metastatic melanoma patients treated with WBRT with ($n = 32$) or without ($n = 91$) concomitant BRAF-I [8]. Grade ≥ 2 radiodermatitis was more frequent in patients receiving combined treatment (44% versus 8%). BRAF-I dose-reduction did not reduce the skin toxicity rate. Vemurafenib was most likely to enhance skin toxicity than Dabrafenib, follicular cystic proliferation only appeared in patients taking Vemurafenib. Nonetheless, no severe late skin-related toxicity was reported. Conversely, no increased skin toxicity and no other severe adverse event was observed with SRS combined with BRAF-I therapy (Table 2).

A case report related a radiation recall in a patient treated with Vemurafenib initiated *after* WBRT completion, while complete response was observed at 3 months [14].

In Narayana et al.'s retrospective study, more than half of the 12 patients were previously treated with ipilimumab (Ipi). The toxicity was not analyzed according to the sequence of Vemurafenib administration, and was reported as low with no intra-tumor hemorrhage (Table 2). In this small series, response rate (RR) appeared improved (complete response: 48%) [15].

In summary, it is not recommended to continue Vemurafenib administration during WBRT; minimally, patients should be closely monitored with early supportive care intervention.

SRS and BRAF-I. Reported toxicities were increased risk of intra-tumor hemorrhage [17] and RN [10, 15, 18, 19] which was not found in all studies; however the follow-up period was too short to actually assess RN risk.

Seven studies or case reports analyzed the safety profile of BRAF-I combined with SRS, with treatment sequencing detailed [10, 16–21]. Five authors reported on 1–24 patients treated with Vemurafenib or Dabrafenib, given *before and during* SRS [10, 16, 17, 20, 21]. Local control (LC) showed mixed results and brain control appeared not improved. Only one case report noticed a severe RN in a melanoma BM patient treated with SRS while on Vemurafenib first line, started 3 months before [10]. Patel et al. [19] analyzed 87 melanoma patients with BM, among whom only 15 were treated with SRS while on BRAF-I. They found significantly increased RN rate in patients submitted to the combined treatment, without improved brain control. Two authors reported on 1, and 17 patients, respectively, treated with *combined BRAF-I and SRS, with a washout period* [21, 22]. Ly et al. noticed

Table 2. RT and BRAF inhibitors

Study	Primary	*n*	RT	Drug	Brain control		Median Survival	Toxicity/type	Median follow-up (months)
Peuvrel et al. [10]	Melanoma	1	SRS	Vemurafenib *Before–during SRS*a	Brain PD	Local NR	9 mo	Severe RN	9
Reigneau et al. [11]	BRAFV600-mutated melanoma	1	WBRT	Vemurafenib *Before–during WBRT*a	NR		NR	Radiation recall (grade 3 skin toxicity)	7
Harding et al. [7]	Melanoma	2	WBRT	Vemurafenib *Before–during WBRT*a	NA		NA	Cutis vercitis gyrate-like skin thickening	4
Schulze et al. [13]	Melanoma	2	WBRT	Vemurafenib *Before–during WBRT*a	NR		NA	Skin toxicity: multiple cystic lesions	3
Lang et al. [9]	BRAFV600-mutated melanoma	1	WBRT	Vemurafenib *Before–during WBRT*a	NA		NA	Cutis vercitis gyrate-like skin thickening	5
Hecht et al. [8]	Melanoma	32	WBRT	Vemurafenib Dabrafenib *Before–during WBRT*a	NR		NR	Increased acute radio-dermatitis (grade 2: 44% versus 8% without BRAFi)	6.6
Rompoti et al. [16]	Melanoma	5	SRS (2) WBRT (3)	Vemurafenib Dabrafenib *Before–during RT*a		NR		Grade 2 skin toxicity in WBRT group	3
Forschner et al. [14]	BRAFV600-mutated Melanoma	1	WBRT	Vemurafenib *After WBRT*	CR		NR	Radiation recall (grade 3 skin toxicity)	3
Narayana et al. [15]	BRAFV600-mutated Melanoma	12	WBRT, PBRT, and/or SRS	Vemurafenib *before/after RT*	Brain 57%	local 75.57%	(OS 6mo) 92%	1 RN (with SRS) 2 intracranial edema	12.2
Ahmed et al. [17]	BRAF V600E-mutated Melanoma	24	SRS	Vemurafenib *Hold for 2–3 days before and after SRS*	(1-y) 23%	(1-y) 75%	7.2 mo	No increased toxicity	5.1
Patel et al. [19]	Melanoma	15	SRS	Vemurafenib Dabrafenib *concurrently*	(1-y) 36.1% (not > SRS alone)	(1-y) 96.7% (not > SRS alone)	(1-y OS) 64.3% (not > SRS alone)	RN rate increased (1-y rate: 28% versus 11% without BRAFi)	6.5
Liebner et al. [18]	BRAFV600E-mutated melanoma	2	SRS SRT	Vemurafenib *After SRT*	NA		NA	RN	4
Gaudy-Marquestre et al. [20]	Melanoma	30	SRS	Vemurafenib 26 Dabrafenib 4 *Before–during (24)* *After (6)*	(6mo) 25%	NR	5.2 mo	No relevant toxicity	6

Continued

Table 2. *Continued*

Study	Primary	*n*	RT	Drug	Brain control		Median Survival	Toxicity/type	Median follow-up (months)
Xu et al. [21]	Melanoma (BRAFV600E-mutated or not)	17	SRS +/- WBRT	Vemurafenib: 12 *During SRS: 2* *After SRS: 10* Dabrafenib: 5 *Washout 8d: 1* *After SRS: 4*	NR	92% (higher than SRS without BRAF-I)	23 mo (versus 8 mo without BRAF-I)	No increased toxicity	3
Ly et al. [22]	BRAFV600-mutated melanoma	17	SRS	Vemurafenib Dabrafenib *before/after SRS, not concurrently*	Not improved	(1-y) 85% (versus 51.5% WT) NS	(1-y OS) 50.2% (versus 45% WT) NS	ITH rate increased	10.5
Wolf et al. [23]	BRAFV600E-mutated melanoma	31	SRS	Dabrafenib: 15 Vemurafenib: 9 Dabrafenib/ Trametinib: 7 *Before SRS: 1* *During SRS: 18* *After SRS: 12*		92.5% (not > WT)	11.2 mo (versus 4.5 mo WT)	No significantly increased ITH (17.9% versus 10.3% WT)	12

[a]BRAF-I were considered administered during radiation therapy when they were administered less than 5 half-lives before or after radiation therapy.

RT, radiation therapy; SRS, stereotactic radiosurgery; SRT, fractionated stereotactic RT; OS, overall survival; WBRT, whole brain radiation therapy; PBRT, partial brain radiation therapy; WT, wild type; RN, radiation necrosis; ITH, intra-tumor hemorrhage; BRAFi, BRAF inhibitor; PD, progressive disease; CR, complete response; NR, not reported; NS, not significant; NA, not applicable.

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in BRAF-I-treated patients, significantly higher intra-tumor hemorrhage rate and higher LC than in patients treated with SRS without inhibitor [22]. Three authors reported on 2–14 patients treated with BRAF-I *after* SRS [18, 20, 21]. Two of them found no relevant toxicity, and improved LC [20, 21], whereas the other reported a RN in a patient previously treated with SRS twice before the initiation of Vemurafenib [18].

Four studies compared patients treated with SRS with or without BRAF-I [19, 21–23]. Two of them reported significantly increased brain-toxicity in the combined treatment arm [19, 22], the two other found no significant difference in intra-tumor hemorrhage rate [21, 23]. Analysis of patients outcomes in these four studies also provided mixed results: LC was not altered by the use of concomitant BRAF-I in two studies [19, 23], and seemed improved in two other studies [18, 21, 22]; BRAF-I had no impact on distant brain control; OS was not altered by the use of concomitant BRAF-I in two studies [19, 22], and was improved in the two other studies [21, 23].

BRAF-I interruption before gamma-knife procedure did not have any impact on toxicity rate [22] and a good safety profile of SRS combined with Dabrafenib and Trametinib (MEK-inhibitor) was reported in a small series of six melanoma patients with BM [24].

In summary, an ongoing BRAF-I treatment can be maintained during SRS, since it would not enhance the toxicity risk. The combination of BRAF-I and SRS, assessed in small and heterogeneous series, showed mixed results relative to both LC and tolerance. Toxicity seemed to be independent of BRAF-I administration sequence. The combination of BRAF-I and SRS, as well as its optimal sequencing, both remain to be assessed.

Tyrosine kinase inhibitors/anti-epidermal growth factor receptor inhibitors

Epidermal growth factor receptor (EGFR) signal transduction pathway activation elicits intracellular signals promoting tumor cells proliferation, differentiation, and survival. There are three main reasons to combine EGFR-inhibitors and RT: (i) EGFR signaling pathway has been identified to induce tumor cells radio-resistance, by several mechanisms, including accelerated tumor clonogen repopulation, reduction of radiation-induced apoptosis [25–27], in tumors with high level of EGFR; (ii) RT has been shown to enhance EGFR signaling pathway [25, 26]; and (iii) many solid tumors show EGFR overexpression, known as prognostic of worse clinical outcome. Thus, the use of EGFR-inhibitors might circumvent the radio-resistance of EGFR-enriched tumors. Pre-clinical studies have suggested a synergistic effect of tyrosine kinase inhibitors (TKIs) and RT combination.

However, clinical studies of combined TKIs and RT are conflicting, relative to efficacy and toxicity, both in retrospective and prospective studies [28–43] (Table 3).

Erlotinib/gefitinib. Four randomized trials compared molecularly unselected non-small-cell lung cancer (NSCLC) patients with BM treated with WBRT (+/− SRS) and TKIs or WBRT (+/− SRS) alone or combined with chemotherapy [32, 37–39]. RR or brain control, as well as OS seemed not improved by TKI delivery, only one study reported improved median survival (13.3 versus 12.7 months, $P < 0.05$) [39]. The RTOG 0320 trial found significantly increased grade 3–5 toxicity rate, whereas the other studies reported a good safety profile.

Four prospective trials found no increased neuro-toxicity when combining TKIs and WBRT [33, 40, 42, 43], two of them reporting improved LC and OS in patients treated with erlotinib and WBRT [40, 43]. Another trial reported significantly higher RR in patients with EGFR-mutant disease (83.33% versus 11.11% in patients with EGFR wild-type disease) [42].

Among six retrospective trials assessing the concomitant use of TKIs and WBRT for NSCLC patients with BM [28, 31, 34–36, 41] only one small retrospective study, including eight patients, reported unexpected systemic toxic effects in half the patients treated with erlotinib combined with WBRT [36]. The authors hypothesized that these toxicities (myelosuppression, mental status changes, respiratory failure) might originate from drug–drug interaction, particularly with steroid and anti-fungal medication. In a case report, Huang et al. [30] described a severe *skin reaction* in the radiation field and bilateral subdural hemorrhage occurring 11 days after WBRT completion in a patient treated with Gefitinib switched for erlotinib without gap during WBRT, with erlotinib maintenance. In a retrospective study, the concomitant use of EGFR-TKI and WBRT was shown to be an independent risk-factor for grade 2 leukoencephalopathy [44].

RR (ranging from 25% to 81%) *were not improved compared with RT alone in none of these studies*; conversely, OS was increased compared with WBRT alone in three of them, although a comparative arm was not always present [28, 34, 41].

Icotinib. The concomitant use of Icotinib and WBRT was found efficient and safe in 20 molecularly unselected NSCLC patients [29], and in a phase I dose-escalating study [45].

Two recent meta-analyses assessed the efficacy and safety of TKIs plus radiotherapy (WBRT/SRS) versus conventional chemotherapy plus radiotherapy or radiotherapy alone [46, 47]. Both meta-analyses found that TKI-group produced significantly higher RR, better median OS, and higher CNS time to progression than non-TKI-group, *at the expense of increased incidence of adverse effects*, especially skin toxicity.

To summarize, the efficacy of TKI concurrently administered with WBRT in molecularly unselected NSCLC BM patients, has not been confirmed in four randomized trials; nonetheless two recent meta-analyses suggest different results. The safety of the combination has been usually reported as acceptable, whereas some studies warned against unexpected 'in field' skin toxicity and a meta-analysis reported higher incidence rate of overall adverse effects, especially rash and dry skin [46]. Consequently, the concurrent use of TKIs with WBRT must be prescribed with caution, particularly with regard to the concomitant use of other medication such as steroids. Moreover, considering not only the EGFR mutational status, but also EGFR-mutation patterns might provide further insight into the role of TKIs and RT in NSCLC BM patients [48].

Multi-kinase inhibitors

RT increases VEGF expression (one of the most important angiogenesis cytokine), as well as it enhances the expression/inhibition of other angiogenesis factors (Ang-2, Ang-1, and their receptor Tie-2), and of tumor growth factors (TGFα, MAPK) [26, 49–51].

Table 3. RT and TKIs

Study	Primary	*n*	RT	Drug	Brain control		Median Survival	Toxicity/type	Median follow-up (months)
RTOG 0320 [38]	NSCLC *EGFR status unknown*	41	WBRT + SRS	Erlotinib *Concurrent with WBRT*	Brain 80%	Local NR	6.1	Grade 3–4: 49% (versus 11% WBRT+SRS alone) Grade 4=BN Grade 5=HS	33.6
Lee et al. [32]	NSCLC *Molecularly unselected*	40	WBRT	Erlotinib *Concurrent with WBRT*	(2 mo) 38.9%	NR	3.4	Increased rash rate (20% versus 5% with placebo)	12.6
Zhuang et al. [43]	NSCLC *Molecularly unselected*	23	WBRT	Erlotinib *Concurrent with WBRT*	NR	(1-y) 91.3%	10.7	Neurotoxicity not increased	NR
Welsh et al. [40]	NSCLC *Molecularly unselected*	40	WBRT	Erlotinib *Concurrent with WBRT*	(1y) 70%	NR	11.8	Grade 3 rash: 15% Neurotoxicity: 5% (1dementia, 1 RN)	28.5
Lind et al. [33]	NSCLC *Molecularly unselected*	11	WBRT	Erlotinib *Concurrent with WBRT*	(3 mo) 100%	NR	4.3	No treatment-related neurotoxicity	3
Olmez et al. [36]	NSCLC *EGFR status unknown*	8	WBRT	Erlotinib*Concurrent with WBRT*	NA	NA	1.5	Unusual grade 3–4 toxicities: 2 grade 3 hepatotoxicity 2 grade 3–4 lymphocytopenia 1 grade 4 neutropenia → † 3 grade 3–5 hyponatremia	3
Lu and Fan [34]	EGFR-mutated NSCLC	39	WBRT	Erlotinib Gefitinib Icotinib *Concurrent with WBRT*	NR	NR	26	No increased toxicity Grade 3–4: Skin: 2.6%, diarrhea: 2.6%, hepatotoxicity: 2.6%, headache: 5.1%	25
Kim et al. [31]	EGFR-mutated NSCLC	18	SRS	Erlotinib Gefitinib		83%	37.1	No increased toxicity	NR

Continued

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Table 3. *Continued*

Study	Primary	*n*	RT	Drug	Brain control		Median Survival	Toxicity/type	Median follow-up (months)
Cai et al. [28]	NSCLC *Molecularly unselected*	65	WBRT	Erlotinib (43) Gefitinib (22) *Concurrent with WBRT*	NR	NR	10.6	No increased toxicity	21
Pesce et al. [37]	NSCLC *EGFR status unknown*	16	WBRT	Gefitinib *Concurrent with WBRT*	NR	NR	6.3	No relevant toxicity	34
Wang et al. [39]	NSCLC *Molecularly unselected*	37	WBRT	Gefitinib *Concurrent with WBRT*	NR	NR	13.3	No relevant toxicity	13.6
Zeng et al. [42]	NSCLC *Molecularly unselected*	15	WBRT	Gefitinib *Concurrent with WBRT*	NR	NR	15.4	No relevant toxicity	15.4
Ma et al. [35]	NSCLC *EGFR status unknown*	21	WBRT	Gefitinib *Concurrent with WBRT*	NR	NR	13	No increased toxicity	15
Zeng et al. [41]	NSCLC *Molecularly unselected*	45	WBRT	Gefitinib *Concurrent with WBRT*	NR	71%	23.4	No increased toxicity	23
Fan et al. [29]	NSCLC *Molecularly unselected*	20	WBRT	Icotinib *Concurrent with WBRT*	NR	NR	14.6	No relevant toxicity	20

RT, radiation therapy; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; NSCLC, non-small cell lung cancer; OS, overall survival; BN, brain necrosis; HS, hemorrhagic stroke; RN, radiation necrosis; NR, not reported; NA, not applicable.

Table 4. Multi-kinase inhibitors and RT

Study	Primary	*n*	RT	Drug	Brain control	Median survival	Toxicity	Median follow-up (months)
Bates et al. [52]	RCC	*25* KI: *7* No KI: *18*	WBRT (5) SRS (2)	Sorafenib Sunitinib Pazopanib temsirolimus	NS	NS	No increased toxicity	NR
Verma et al. [56]	RCC	*81* KI: *40* No KI: *41*	SRS	Sorafenib Sunitinib Before BM After BM No TKI	 1-y: 53% 1-y: 90% 1-y: 74%	Better in patients receiving TKI at the onset of BM	No increased toxicity	5.4
Cochran et al. [53]	RCC	61 KI: *24* No KI: *37*	SRS	TKI mTORi bevacizumab	1-y LC: 93.3% (versus 60% without TT)	16.6 mo (versus 7.2 mo without TT)	No increased toxicity	NR
Staehler et al. [54]	RCC	*51*	SRS	Sorafenib (29) Sunitinib (22)	1-y: 100% 2-y: 96.6%	11.1 mo	3 seizures 1 BH gr5	14.7
Staehler et al. [55]	RCC	*3*	WBRT	Sunitinib	NR	NR	No increased toxicity	14.3
Wuthrick et al. [58]	multiple	*15*	WBRT PBRT	Sunitinib	NR	NA	2 grade 3 fatigue	34.2
Langrand-Escure et al. [57]	RCC	*20*	WBRT	Sunitinib Sorafenib Axitinib mTORi bevacizumab	NR	NR	2 grade 3: Confusion IHT	9.5

BH, brain hemorrhage (supposed due to systemic progression); IHT, intracranial hypertension; RT, radiation therapy; RCC, renal cell carcinoma; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; PBRT, partial brain radiotherapy; NR, not reported; NS, not significant; NA, not applicable; TKI, tyrosine kinase inhibitors; mTORi, mammalian target of rapamycin inhibitors.

In murine experimental models, low doses of ionizing radiation have indeed been shown to promote tumor growth and metastasis through VEGFR2 activation. Prior use of TKI targeting VEGFR prevented this effect [50].

Data from retrospective studies assessing the multi-kinase inhibitors (mKI) impact on LC and survival are conflicting [52–56] (Table 4). Nonetheless, they all agree on a good toxicity profile of the combination, allowing the continuation of this systemic treatment when brain RT is considered.

Three studies retrospectively compared BM patients treated with brain RT with or without mKI [52, 53, 56]. Whatever the RT scheme (WBRT, SRS, or both), the combined therapy was safely administered without significantly increased toxicity compared with patients treated with RT alone. Concurrent mKI use seemed to improve LC in only one out of these three studies [53], improving median survival in two reports [53, 56]; in the Verma et al.'s study, there was an imbalance for further systemic treatment between the groups [56]. An improved OS was observed only in the group taking TKI *at the onset* of BM, but not in those developing BM while on mKI.

Four other studies retrospectively analyzed BM patients treated with brain RT and combined KI, without control group [54, 55, 57, 58]. Two of them found that both SRS and WBRT did not enhance the adverse effects of mKI, although one among 22 patients treated with sunitinib and SRS experienced fatal bleeding while on treatment with sunitinib 3 months after SRS [54, 55]. In one another study, 7 out of 15 patients (47%) experienced grade 3 toxicity, only two were thought to be attributable to the combination treatment (fatigue) [58]. The fourth study reported two grade 3 toxicities (10%) in patients treated with mKI and WBRT (one confusional state, and one intracranial hypertension). Two trials reporting RRs found excellent LC with SRS-mKI combination, whereas sunitinib and WBRT combination achieved partial response in 20% of patients [54, 58].

In summary, there is no definitive argument to conclude on the efficacy/toxicity ratio of RT and mKI.

Anti-angiogenic agents

The combination of anti-angiogenic agents with RT had initially been avoided due to the potential risk of brain hemorrhage. Subsequently, some studies (particularly in primary brain tumors), proved its safety, with some efficacy on tumor control. The anti-angiogenic agents and RT combination was thus considered with the objective to increase tumor brain control.

Anti-angiogenic agents mainly act through vascular endothelial growth factor (VEGF) inhibition. Their objective is to deprive the tumor of oxygen and nutrients. However, many other

signaling pathways, some of them radiation-activated, are able to promote angiogenesis, thus, the optimal use of anti-angiogenic agents, including as radiosensitizers, remains a wide field to be elucidated. Experimental studies showed that the advantage of antiangiogenic agents given concomitantly with RT partly relies on their ability to modify the neo-vasculature structure, becoming less 'anarchic', at least during a critic period (named 'normalization window'), in which hypoxia could be decreased, allowing enhancement of RT anti-tumor activity [59, 60]. Other mechanisms leading to increased tumor cells apoptosis have also been described [61, 62].

Bevacizumab combined with focal brain RT has been shown to improve progression-free survival in primary brain tumors [63, 64]. Its efficacy and safety profile have been suggested in a phase I study when combined with WBRT in BMs patients [65]. To our knowledge, there is no more advanced study relative to this treatment combination in the setting of BMs.

Anti-HER2

Trastuzumab. Curie Institute retrospectively assessed 31 HER2+ breast cancer (BC) patients with BMs receiving WBRT and Trastuzumab concomitantly [66]. The median time to progression was 10.5 months. A complete resolution of symptoms was observed for 74.2% of the patients. Six patients (19.4%) had a complete radiological response, and partial response was achieved in 17 patients (54.8%). Treatment was well tolerated, only 7 patients (23%) had nausea grade 1 and 2, asthenia and headache. The passage of Trastuzumab through the blood–brain barrier into the cerebrospinal fluid (CSF) could be improved after radiotherapy. Stemmler et al., found a ratio serum/CSF of 420 : 1 in 5 patients irradiated in the brain against 76 : 1 in 3 patients without brain RT [67]. These results suggest a potential tumor response benefit of trastuzumab continued during radiotherapy.

Lapatinib. A phase 1 trial attempted to define the maximum tolerated dose of concurrent lapatinib with WBRT. This trial was not conclusive due to important toxicity other than neurologic. However, among 28 assessable patients, the brain objective RR was 79% [68]. The data of the phase II WBRT concurrently administered with lapatinib in patients with BM from HER2+ BC are pending for 2018.

Yomo et al. [69] retrospectively analyzed 40 HER2+ BC patients treated with ($n = 26$) or without ($n = 14$) lapatinib. The median follow-up time after SRS was 10.3 months. There was no significant difference in OS between the two groups but the lapatinib group was associated with an improved 1-year LC rate (86% versus 69%; $P < 0.001$), which *suggests a synergic action of lapatinib and SRS*. Tolerance was acceptable.

T-DM1. There is a strong rationale supporting the combination of antibodies–drug conjugates (ADCs) and RT, since ADCs are considered to specifically target cancer cells (overexpressing targeted antigen).There is no pre-clinical available data about the combination of radiotherapy and T-DM1. Clinical data remain scarce, mainly based on case reports. While T-DM1 associated with WBRT showed encouraging RR without side-effects [70, 71], three case reports raised the problem of recall effect in patients previously treated with SRS, then with T-DM1 [72–74]. Carlson et al. reported a high number of significant RN, in a series of seven patients with BM from HER2+ BC, treated with T-DM1 and SRS. Four out of seven patients experienced shortly after T-DM1 infusion, a symptomatic cerebral edema. One patient had to undergo resection of a metastasis and pathology revealed severe RN with no viable tumor cells [72]. Recently, Mitsuya et al. reported on two cases of RN aggravation, far away from SRS delivery, at the time of T-DM1 initiation [74]. A significant number of RN has been reported in a series of eight patients treated with T-DM1 concomitant with SRS for HER2+ BC BM.

In summary, keeping in mind the paucity of data, LC was commonly improved with anti-HER2 agents associated with RT, but, whereas the association of Trastuzumab and RT has not shown any tolerance issue, as well as lapatinib combined with SRS or T-DM1 combined with WBRT, concomitant delivery of SRS with T-DM1 or lapatinib with WBRT should require caution [68, 73].

RT and immune checkpoint blockade

RT is well known to induce immunological changes both in the tumor and in its microenvironment (through the promotion of effector immune cells recruitment), and to potentially induce systemic responses due to anti-tumor immunity promotion ('abscopal' effect), via several mechanisms, including enhancement of tumor antigens release, exposure of novel tumor antigens, increase of immunogenic cell death, and increase of pro-inflammatory cytokines activating T cells [75]. Through its action, particularly on the tumor microenvironment, RT might 'facilitate' immunotherapies such as ICI, but has also immunosuppressive effects [75]. Recent pre-clinical studies have suggested a synergy between RT and immunotherapies [76–79], potentially more efficient when ICI is not delayed after the RT completion [76]. The efficiency of RT and ICI combination is currently under investigation, in order to identify the optimal timing of the combination, the optimal RT dose per fraction and the effect of the combination according to the irradiated site [80].

Most available clinical studies are retrospective. They included melanoma BM patients, mainly treated with Ipi (a fully human monoclonal antibody that promotes anti-tumor T cells) and RT (mainly SRS). These studies suggested an increased OS with the combined treatment (specifically when Ipi was administered concurrently with RT), without increased toxicity, *although delayed RN, intra-tumor hemorrhage and edema remain to be fully assessed* [81–87] (Table 5).

SRS+/− Ipi

Four studies retrospectively compared patients treated with SRS with or without Ipi [83–86]. Three of them compared LC, as well as toxicity and response rates [84–86]. RRs as well as toxicity were similar between patients treated with SRS with or without Ipi. All the four studies compared median survivals; two of them found comparable survival outcomes [84, 85]; two other studies found improved median survival in patients treated with Ipi, possibly *suggesting that an optimal timing of the combination might have an impact* on patient outcome.

Four studies investigated the impact of Ipi administration timing relative to RT [82, 83, 85, 86]. Two studies found *a positive*

Table 5. Immune checkpoint Inhibitors and RT

Study	Primary	*n*	RT	Drug	Brain control		Median survival	Toxicity	Median follow-up (months)
Patel et al. [85]	Melanoma	*20*	SRS	Ipilimumab *1 during SRS* *12 before SRS* *7 after SRS*	Not improved versus SRS alone		Not improved versus SRS alone (8 versus 9.1 mo)	No increased toxicity	7.3
Knisely et al. [83]	Melanoma	*77*	SRS	Ipilimumab 27 +SRS: *11 before SRS* *16 after SRS*	Brain 37%	local NR	21.3 mo (versus 4.9 without ipi) No ≠ before/after	NR	NR
Silk et al. [86]	Melanoma	*70*	WBRT (16) SRS (17)	Ipilimumab 33 +RT: *12 before RT* *21 after RT*	Not significantly increased in Ipi group		18.3 mo (versus 5.3 without ipi) 8.1 mo 18.4 mo	No neuro-toxicity (ipi)	10
Mathew et al. [84]	Melanoma	*58*	SRS	Ipilimumab 25 + SRS *4 before SRS* *7 during SRS* *10 after SRS*		65%	(OS 6 mo) 56%	No increased toxicity	6
				33 without ipi		63%	46% (NS)		
Kiess et al. [82]	Melanoma	*46*	SRS	Ipilimumab *15 during SRS,* *19 before SRS,* *12 after SRS*	brain 31% 36% 8%	Local 100% 87% 89%	(1-y OS) 65% 56% 40%	*during* SRS : no relevant toxicity *before* SRS: ITH (13%/0[a]), seizure (13%/0[a]) *after* SRS: ITH (6/3[a])	22
Tazi et al. [87]	Melanoma	*10*	SRS	Ipilimumab *During or after SRS*			16.5 mo 3-y OS: 50%	No increased toxicity	NR
Gerber et al. [88]	Melanoma	*13*	WBRT	Ipilimumab *4 before WBRT* *6 during WBRT* *3 after WBRT*	56%		4 mo	1 grade 3 cognitive change 100% new or worsening ITH	4
Cohen-Inbar et al. [89]	Melanoma	*46*	SRS	Ipilimumab *14 before SRS* *32 during/after SRS*	33.6% 50.4%	16.5% 72.6%	6.4 mo 13.8 mo	RN and post-SRS edema increased when Ipi was administered during or after SRS	7.9
Alomari et al. [90]	Melanoma NSCLC	*2*	SRS	Pembrolizumab Nivolumab + ipilimumab	100%		NA	pseudo clinical and radiological progression	6
Ahmed et al. [91]	Melanoma	*26*	SRS	Nivolumab *During (washout 6d)/ before/after*	(1-y) 53%	(1-y) 85%		ITH: 5% Grade 3 oedema: 10%	9.4

[a]x%/x%= grade 3/grade 4.

ipi, ipilimumab; RT, radiation therapy; SRS, stereotactic radiosurgery; OS, overall survival; WBRT, whole-brain radiation therapy; NSCLC, non-small-cell lung cancer; NR, not reported; NS, non-significant; NA, not applicable; ITH, intra-tumor hemorrhage.

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Table 6. Ongoing trials of RT combined with TT or ICB

Pharmaceutic class	Study reference	RT scheme and drug	Title	State
BRAF-I	NCT01721603	SRS, dabrafenib	A phase 2 prospective trial of dabrafenib with stereotactic radiosurgery in BRAFV600E melanoma brain metastases	Completed
	NCT02974803	SRS, dabrafenib and trametinib	Concurrent dabrafenib and trametinib with sterotactic radiation in patients with BRAF mutation-positive malignant melanoma and brain metastases	Not yet recruiting
TKIs	NCT01130779	WBRT/SRS, erlotinib	The continuation of erlotinib	Unknown
	NCT02882984	WBRT/HFSRS, gefitinib/tarceva/lcotinib	Hypofractionated brain radiation in EGFR-mutated adenocarcinoma cranial disease (hybrid)	Recruiting
	NCT01234740	WBRT/SRS, bafetinib	Bafetinib in treating patients with recurrent high-grade glioma or brain metastases	Completed
Multi-KI	NCT00981890	SRS, sunitinib	Stereotactic radiosurgery with sunitinib for brain metastases	Active, not recruiting
	NCT02019576	SRS, sunitinib	Stereotactic radiotherapy for metastatic kidney cancer being treated with sunitinib	Recruiting
	NCT01276210	SRS, sorafenib	Sorafenib tosylate and stereotactic radiosurgery in treating patients with brain metastases	Active, not recruiting
	NCT02132598	WBRT/SRS, cabozantinib	Trial of cabozantinib (XL184) in non-small cell lung cancer with brain metastases	Recruiting
Antiangiogenic agents	NCT02672995	SRS, bevacizumab	Fractionated stereotactic radiosurgery with concurrent bevacizumab for brain metastases: a phase I dose-escalation trial	Recruiting
	NCT02162537	WBRT/SRS, cisplatine-permetrexed-bevacizumab	Multicentric, randomized, Phase III Trial Comparing 2 strategies in patients with non-squamous non-small cell lung cancer with asymptomatic	Recruiting
Anti-HER2	NCT01622868	WBRT/SRS, lapatinib ditosylate	Whole-brain radiation therapy or stereotactic radiosurgery with or without lapatinib ditosylate in treating patients with brain metastasis From HER2-positive breast cancer	Recruiting
Anti-CTLA4	NCT02097732	SRS, ipilimumab	Ipilimumab induction in patients with melanoma brain metastases receiving stereotactic radiosurgery	Active, not recruiting
	NCT02662725	SRS, ipilimumab	Ipilimumab combined with a stereotactic radiosurgery in melanoma patients with brain metastases	Completed
	NCT01703507	SRS, ipilimumab	Phase I Study of Ipilimumab Combined With Whole Brain Radiation Therapy or Radiosurgery for Melanoma	Active, not recruiting
	NCT01950195	SRS, ipilimumab	A Pilot Study of stereotactic radiosurgery combined with ipilimumab in patients with newly diagnosed melanoma metastases in the brain and spine	Terminated
	NCT02107755	SRS, ipilimumab	Stereotactic radiation therapy and ipilimumab in treating patients with metastatic melanoma	Active, not recruiting
Anti-PD-1	NCT02716948	SRS, nivolumab	A Pilot Study of stereotactic radiosurgery combined with nivolumab in patients with newly diagnosed melanoma metastases in the brain and spine	Recruiting
	NCT02696993	SRS/WBRT, nivolumab/ipilimumab	Trial of nivolumab with radiation or nivolumab and ipilimumab with radiation for the treatment of intracranial metastases from non-small cell lung cancer	Recruiting
	NCT02978404	SRS, nivolumab	Combining radiosurgery and nivolumab in the treatment of brain metastases	Not yet recruiting
	NCT02858869	SRS, pembrolizumab	Pembrolizumab and stereotactic radiosurgery for melanoma or non-small cell lung cancer brain metastases	Recruiting
	NCT02886585	SRS, pembrolizumab	Pembrolizumab in central nervous system metastases	Recruiting
Anti-PD-L1	NCT02669914	WBRT/SRS, durvalumab	MEDI4736 (durvalumab) in patients with brain metastasis from epithelial-derived tumors	Recruiting

impact on survival in patients treated with Ipi during or after RT [82, 86]. One study found that OS seemed improved in patients treated with Ipi within 14 days of RT [85], and another study found no difference in survival whether the drug was started before or after SRS [83].

Studying 46 patients treated with SRS plus Ipi, Kiess et al. [82] observed an increase in BM diameter in 50% of patients receiving Ipi during or after SRS (in patients receiving Ipi after SRS, BM increase occurred only after Ipi introduction). Grade 3 and 4 toxicities were observed in 20% of patients (Table 5), and were slightly more frequent in patients receiving Ipi during SRS.

Ipi+/− SRS

One study retrospectively compared 31 patients treated with Ipi with or without SRS [87]. The authors found no increased toxicity with the addition of SRS to Ipi, and no median survival difference between the two groups.

Clinical reports without 'comparison' arm

Du Four et al. reported on three patients experiencing an RN after brain RT (SRS with or without WBRT), combined with Ipi started either before or a few months after RT [81]. Gerber et al. retrospectively analyzed 13 patients treated with concurrent WBRT and Ipi (within 30 days of one another) [88]. Only early toxicity was reported. They observed one grade 3 cognitive change during WBRT in a patient suffering from acute seizure and subsequent hemorrhage during WBRT. All patients with follow-up imaging had new or worsening (mainly asymptomatic) intra-tumor hemorrhage, leading the authors to require further prospective studies of combined WBRT and ipi. Recently, Cohen-Inbar et al. reported a retrospective series of 46 patients, strongly suggesting that *delivering SRS before or during Ipi treatment could enhance both efficacy and toxicity* [89].

In summary, the retrospective design of these small sample size series does not allow either to definitely conclude on the impact of Ipi on the survival of melanoma BM patients treated with RT, or to categorically indicate an optimal administration sequence. Nonetheless, giving the amount of evidence that RT acts as an immune-modulator, and on the fact that a limited proportion of patients will respond to ICI alone, the combination of RT and ICI deserves intensive further exploration, and results of ongoing studies are eagerly awaited.

Two retrospective studies reported the outcome of BM patients treated with SRS and PD-1 (Programmed death-1) monoclonal antibodies (mAb) (targeting the PD-1 human cell-surface receptor, expressed on activated T-cells, and leading to T-cell effector function suppression when engaged by its ligand) [90, 91]. In two cases of patients treated with SRS followed by PD-1 mAb therapy (Pembrolizumab or Nivolumab + Ipi), Alomari et al. observed, shortly after PD-1 mAb introduction, a clinical and radiological pseudo-progression of the recently treated BM, which, on pathologic examination, proved to be radiation-induced changes with no viable tumor cells, assumed to be an accelerated response to SRS [91]. The concomitant use of PD-1 mAb and SRS has been suggested to improve distant intra-cranial control compared with the concomitant use of anti-CTLA4 and SRS, this remains to be confirmed [90]. Interestingly, but using a debatable endpoint, (the 'early radiographic response'), Qian et al. [92] suggested different profiles of response combining SRS with Ipi *versus* nivolumab and pembrolizumab.

Discussion

Conclusion

Overall, studies assessing RT and systemic agent combination are currently mainly focused on the concomitant use of TT or ICI and SRS, since SRS nowadays seems to supplant WBRT in BM RT. Most of available studies appear to advocate for TT or ICI combination with RT, without altering the clinical safety profiles, allowing the maintenance of systemic treatments when SRS is considered. Moreover, RR assessment has to be standardized, better using the Response Assessment in Neuro-Oncology (RANO) group [93], to actually assess the impact of combined therapies. Further investigations are warranted, with longer follow-up, and better understanding of RT-immune effects. Numerous prospective studies are ongoing (Table 6), with the objective to better define the safety of these combinations. Cognitive functions, health-related quality of life and RN risk remain to be assessed. The results of prospective studies are awaited in order to complete and validate the above discussed retrospective data.

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