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Use of Systemic Therapy Concurrent With Cranial Radiotherapy for Cerebral Metastases of Solid Tumors

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Brain metastases • Radiotherapy • Systemic therapy • Molecular targeted agents • Monoclonal antibodies • Toxicity

Abstract

The incidence of brain metastases of solid tumors is increasing. Local treatment of brain metastases is generally straightforward: cranial radiotherapy (e.g., whole-brain radiotherapy or stereotactic radiosurgery) or resection when feasible. However, treatment becomes more complex when brain metastases occur while other metastases, outside of the central nervous system, are being controlled with systemic therapy (chemotherapeutics, molecular targeted agents, or monoclonal antibodies). It is known that some anticancer agents can increase the risk for neurotoxicity when used concurrently with radiotherapy. Increased neurotoxicity decreases quality of life, which is undesirable in this predominantly palliative patient group. Therefore, it is of utmost importance to identify the compounds that should be temporarily discontinued when cranial radiotherapy is needed.

This review summarizes the (neuro)toxicity data for combining systemic therapy (chemotherapeutics, molecular targeted agents, or monoclonal antibodies) with concurrent radiotherapy of brain metastases. Because only a limited amount of high-level data has been published, a risk assessment of each agent was done, taking into account the characteristics of each compound (e.g., lipophilicity) and the microenvironment of brain metastasis. The available trials suggest that only gemcitabine, erlotinib, and vemurafenib induce significant neurotoxicity when used concurrently with cranial radiotherapy. We conclude that for most systemic therapies, the currently available literature does not show an increase in neurotoxicity when these therapies are used concurrently with cranial radiotherapy. However, further studies are needed to confirm safety because there is no high-level evidence to permit definitive conclusions. *The Oncologist* 2017;22:222–235

Implications for Practice: The treatment of symptomatic brain metastases diagnosed while patients are receiving systemic therapy continues to pose a dilemma to clinicians. Will concurrent treatment with cranial radiotherapy and systemic therapy (chemotherapeutics, molecular targeted agents, and monoclonal antibodies), used to control intra- and extracranial tumor load, increase the risk for neurotoxicity? This review addresses this clinically relevant question and evaluates the toxicity of combining systemic therapies with cranial radiotherapy, based on currently available literature, in order to determine the need to and interval to interrupt systemic treatment.

Introduction

Systemic treatment options for metastasized solid tumors have increased [1–6]. Thus, long-term progression-free survival can sometimes be achieved, especially when a driver oncogene in the tumorigenesis of a specific tumor can be targeted, such as *BRAF* V600E in melanoma. Moreover, radical treatment for patients with oligometastatic disease has become an accepted treatment modality [7]. With a growing number of long-term cancer survivors, brain metastases are frequently observed, especially in patients with non-small cell lung cancer (NSCLC), breast cancer, melanoma, and renal cell carcinoma (RCC) [8].

Some systemic treatment schedules (chemotherapeutics, targeted agents, and monoclonal antibodies) show intracranial response and/or stabilization of brain metastases [9, 10]. Contrary to traditional chemotherapeutical agents, recently developed targeted agents show the potential to cross the blood-brain barrier (BBB). These targeted agents may be able to

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control brain metastases, especially when the brain metastases are relatively small and asymptomatic [1]. However, despite initial responses, brain metastases often progress during systemic treatment. Traditionally, whole-brain radiotherapy (WBRT) is the cornerstone of the treatment of symptomatic multiple (four or more) brain metastases. The use of partial-brain radiation therapy techniques, including but not limited to stereotactic radiosurgery (SRS) and stereotactic radiotherapy, has increased and is the preferred initial treatment option in patients with a limited number of (one to three) brain metastases smaller than 4 cm [2]. Depending on national guidelines, number, size, and leptomeningeal spread of the brain metastases, cranial radiotherapy is the treatment modality of choice.

Some chemotherapeutics and targeted agents have shown to be radiosensitizing for healthy brain tissue, which may increase the risk for complications. These complications have mainly been described in the extracranial setting (e.g., bleeding, bowel perforation, radionecrosis) and resulted in severe morbidity and impaired quality of life [11–13].

To minimize the risk for neurotoxicity, systemic therapies are often discontinued during cranial radiotherapy. However, the disadvantage of discontinuation is a potential tumor flare of extracranial disease. Ninety-seven percent of systemically administered oncolytic drugs is eliminated from the blood after 5 times the half-life ($t_{1/2}$). Because of the long $t_{1/2}$ of most targeted agents (or their active metabolites) and monoclonal antibodies, this would mean a long period (weeks to months) of discontinuation when this level of elimination is pursued, which is undesirable in the control of extracranial tumor load. Additionally, 97% of drug excretion might not be sufficient to abolish the metabolic activity of these agents in brain metastases.

The aim of this review is to determine which of the commonly used systemic therapies can be safely continued during cranial radiotherapy and which should be discontinued, based on the currently available literature. We discuss the chemotherapeutics, targeted agents, and monoclonal antibodies that are most commonly used in the subset of solid tumors that most frequently metastasize to the brain.

Materials and Methods

Systemic therapies that are commonly used in the treatment of tumors that metastasize to the brain were selected for inclusion. The search was conducted on papers describing the combination of these systemic agents and cranial radiotherapy of cerebral metastases of solid tumors. Additional literature describing the ability of the systemic therapy to penetrate the BBB and pharmacological characteristics was gathered as supportive information. With these data, a narrative review was executed, as this is the best review format that can be obtained considering the available information.

Inclusion and Exclusion Criteria

Papers describing the combination of cranial radiotherapy and one of the selected systemic therapies and having (neuro)toxicity as an outcome measure were eligible for inclusion. All types of articles (including reviews; case reports; and phase I, II, and III studies) were included.

Papers describing the treatment of primary brain tumors were excluded. All non-English-language articles were excluded.

Additional literature was searched on combined chemotherapeutic schedules because literature on separately used chemotherapeutics was very scarce. However, this was not part of the main search strategy.

Identification of Studies

The literature search was conducted independently by two researchers (M.V. and H.M.) up to June 2015 using the databases PubMed, MEDLINE, Cochrane, and Web of Science. References from the included studies were also reviewed for eligible literature. The complete search strategy can be found in the supplemental online data (Appendix A).

Study Selection

Studies were initially selected on the basis of title; further selection took place according to the abstracts. For articles found to be eligible, the whole article was read. Eligibility was assessed by two reviewers (M.V. and H.M.). Disagreements were resolved by consensus.

Data Extraction

From the included papers, data were extracted on (a) trial characteristics; (b) treatment schedule used; and (c) the described neurotoxicity, methods of evaluating toxicity, assessment of quality of life (QoL) and neurocognition, and follow-up characteristics.

Results

An overview of the trial characteristics can be found in the supplemental online data (Appendix B). Working mechanisms of the discussed systemic therapies are reported in Appendix C of the supplemental online data. Table 1 describes pharmacological characteristics of the systemic agents discussed in this review. Table 2 describes all reported neurotoxicity.

A total of 2,172 records were identified by using the search strategy (Appendix A). In the end, 37 articles were included in the review. Figure 1 provides an overview of the complete selection process.

Combination of Radiotherapy and Chemotherapy

Antimetabolites: Capecitabine/5-Fluorouracil and Gemcitabine

Two studies describe toxicity (Table 2) of capecitabine used concurrently with cranial radiotherapy. One study reported overall mild toxicity and no high-grade neurotoxicity [14]. A second study, a phase II trial, in which capecitabine was combined with WBRT followed by sunitinib, closed early because of low efficacy and excessive toxicity, although no high-grade neurotoxicity was mentioned [15]. Neurocognitive impairment and QoL, both salient endpoints, were not separately scored in these studies.

Two trials investigated toxicity (Table 2) for the combination of gemcitabine and cranial radiotherapy. A phase I trial reported dose-limiting toxicity at the highest dose level (70 mg/m^2 twice weekly) to be grade IV neutropenia. No significant nonhematological toxicities were observed at any dose level. Moreover, no deterioration in mental function was observed by the Folstein test [16]. In another phase I trial, dose-limiting neurotoxicity was observed, at a dose of 700 mg/m^2, consisting of grade III seizures and grade II muscle weakness [17]. Neither study scored for QoL. Additionally, gemcitabine-induced radiation recall, a serious inflammatory reaction often leading to necrosis, has been described. Radiation recall reactions were seen in the central

Table 1. Pharmacological characteristics of systemic therapies

Oncolytic	$t_{1/2}$	Main excretory pathway % (within timeframe)	Prodrug	Active metabolites	Intact BBB penetration MW and lipophilicity	Fraction protein unbound CSF/plasma concentration or % penetration	References
Capecitabine	45–70 min	R 84% 24 h; 96% 7 d	Yes	5′-DFCR, 10 min; 5′-DFUR, 20 min; fluorouracil, within 45 min, mainly at tumor site; further metabolized to active metabolites FdUMP and FUTP and to inactive metabolite FBAL	Yes; MW 359 g/mol; XlogP3 = 0.6	Breast cancer brain metastases/serum ratio capecitabine, 0.28% (0.031%–0.81%); 5-FU, 5.64% (1.67%–12.9%)	[81–84]
Carboplatin	2–3 h free ultrafiltrable platinum and carboplatin; 4–6 d total platinum	R 71% 24 h	No	Carboplatin undergoes intracellular hydrolysis to form reactive platinum complexes; 5.8 ± 1.6 d (total platinum, including protein-bound fraction)	Limited; MW 371 g/mol	Low tissue-to-blood ratio	[85–87]
Cisplatin	23–54 min free ultrafiltrable platinum; 2–5 d total platinum	R > 90% 25% 24 h		Platinum analog	Not readily; MW 300 g/mol	Unknown	
Docetaxel	11 h	B/F 80% 48 h	No	NA	Limited, relatively low levels, but large interpatient variation; MW 808 g/mol; XLogP3 = 1.6	Fraction unbound in CSF 67%–103%; ratio total (CSF to plasma) 0.01%–0.6%, protein bound, 0.1%–9% ($\sim IC_{50}$)	[88]
Gemcitabine	0.7–1.6 h (infusion <30 min)	R 92%–98% 1 wk 89% as dFdU	Yes	dFdC undergoes intracellular activation to pharmacologically active dFdCDP and dFdCTP and metabolic inactivation to dFdU metabolite	Unknown; MW 300 g/mol	Believed to cross, if disrupted	
Paclitaxel	2.5 h (3-h infusion 175 mg/m²) extravascular distribution: longer terminal $t_{1/2}$	B/F 71%	No		Limited; MW 854 g/mol; XLogP3 = 2.5	Brain tumor tissue concentrations were in therapeutic range in 3 patients but low in another patient; difference possibly related to BBB disruption;metastatic brain tumors had higher paclitaxel concentrations in the tumor center (1.93-fold, p = .10) and in tumor periphery (2.46-fold, p = .039) compared with primary brain tumors	[89, 90]
Sunitinib	40–60 h	F 61%	No	Desethyl metabolite SU12662 (similar potency to that of sunitinib) 80–110 h	Seems able to cross BBB in small amounts; MW 398 g/mol; XLogP3 = 2.6	Only animal (mice) studies available	[105]
Sorafenib	25–48 h	F 77%	No	Pyridine-*N*-oxide (similar potency to that of sorafenib)	Limited, based on animal studies; MW 465 g/mol; XLogP3 = 4.1	Only animal (mice/monkey) studies available: rhesus monkeys: CSF penetration of sorafenib was 0.02% and 3.4% after correcting for plasma protein binding	[106]

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Table 1. (continued)

Oncolytic	$t_{1/2}$	Main excretory pathway % (within timeframe)	Prodrug	Active metabolites	Intact BBB penetration MW and lipophilicity	Fraction protein unbound CSF/plasma concentration or % penetration	References
Erlotinib	36.2 h	B/F 90%	No	OSI-420 and OSI-413 present in plasma at levels <10% of erlotinib and display similar pharmacokinetics as erlotinib	Yes, partially; MW 393 g/mol; XLogP3 = 3.3	2.0% ± 0.5% in combination with cisplatin/pemetrexed; erlotinib only 2.3% ± 0.2% − 2.77%–5.1% also 4.4% ± 3.2% found without WBRT; pulsatile (intermittent) erlotinib 1,000–1,500 mg weekly: penetration rate 1.15% but CSF concentration > IC_{50}	[83, 91–95]
Gefitinib	30.5–41 h	F 86%	No	0-desmethyl-gefitinib (1/14 the potency of gefitinib)	Yes, partially; MW 447 g/mol; XLogP3 = 4.1	Mean ratio CSF/total plasma concentration 1.3% ± 0.7%; CNS penetration closer to 50% when one accounts for available free drug; penetration rate in CSF 1.13% ± 0.36%. Concentration in CSF distinctly less than its IC_{50}	[87, 91, 92, 96, 97]
Lapatinib	24 h	F up to 67%	No	NA: activity not characterized	Limited; MW 581 g/mol; XLogP3 = 5.1	~50 fold; uptake demonstrated in nonirradiated breast cancer brain metastatic tissue (pulsatile lapatinib): breast cancer brain metastases: serum ratio: 0.19%–9.8%	[83, 84, 98, 107]
Vemurafenib	30–120 h	F 94%	No	NA, or activity not characterized yet	Generally limited; MW 490 g/mol; XLogP3 = 5.0	CSF: plasma concentration ratio 0.98% ± 0.84%	[99–101]
Ipilimumab	14.7–15.6 d	TMD	No	NA	Unlikely; however, activated T cells might do so; MW 148 kDa	Penetration unlikely based on MW	[105]
Trastuzumab	28–38 d (washout till 27 wk)	TMD	No	NA	Without a compromised BBB, trastuzumab is thought to have limited access	Penetration unlikely based on MW	[102, 107]
Bevacuzimab	18–20 d; shortest for women	TMD	No	NA	Unlikely, but possible (VEGF might manipulate BBB integrity); MW 149 kDa	Penetration unlikely based on MW	[103, 104]

Abbreviations: 5′-DFCR, 5′-deoxy-5-fluorocytidine; 5′-DFUR, 5′-deoxy-5-fluororuidine; BBB, blood-brain-barrier; B/F, biliary and/or fecal excretion; CSF, cerebrospinal spinal fluid; d, day(s); dFdC, 2′,2′-difluoro-2′-deoxycytidine; dFdCDP, 2′,2′-difluoro-2′-deoxycytidin diphosphate; dFdCTP, 2′,2′-difluoro-2′-deoxycytidine; dFdU, 2′,2′-difluorodeoxyuridine; F, fecal excretion; FBAL, α-fluoro-β-alanine; FdUMP, 5-fluorodeoxy-uridine-5-monophosphate; FUTP, fluorouridine-5-triphosphate; h, hour(s); IC_{50}, half maximum inhibitory concentration (measure of how much of a drug is needed to inhibit a certain biological process by half); MW, molecular weight; NA, not available; R, renal excretion; $t_{1/2}$, half-life; TMD, target-mediated deposition; VEGF, vascular endothelial growth factor; WBRT, whole-brain radiation therapy.

nervous system, skin, gastrointestinal tract, and lymphatic and musculoskeletal systems. The time between initiation of radiation and recall of the radiation phenomenon ranged from 3 weeks to 8 months from the time gemcitabine was initiated. The usual dosage of gemcitabine in these cases was 1,000 mg/m^2 given weekly [18–20].

Platinum Analogs: Cisplatin and Carboplatin
One study described the toxicity (Table 2) of cisplatin combined with cranial radiotherapy. In this study, 4 of 14 patients had

possible central nervous system toxicity, categorized as neurological deterioration and seizure. However, in all 4 patients other possible reasons for the transient neurologic deterioration were present, such as tapering of corticosteroids [21].

Cisplatin combined with other chemotherapeutic agents did not cause significant neurotoxicity when used concurrently with radiotherapy. Several studies describe cerebral radiotherapy in combination with cisplatin and other chemotherapeutics, such as vinorelbine and ifosfamide [22, 23] vindesine and mitomycin [24], pemetrexed [25, 26], vinorelbine [27], and

Table 2. Overview of reported toxicity with concurrent use of systemic therapies and cerebral radiotherapy

Regimen	Author, year	Reported neurotoxicity	Method of evaluating toxicity	Follow-up toxicity characteristics
Chemotherapy				
Capecitabine	Chargari et al., 2009	Grade I nausea and headache. No severe neurotoxicity.	RTOG radiation morbidity scoring system	Gadolinium-enhanced MRI or CT, 6 wk after treatment and in case of neurologic symptoms. Medical interview and clinical examination every 3 mo.
	Niravath et al., 2015	No significant neurotoxicity	Not described	Not described
Gemcitabine	Maraveyas et al., 2005	No significant neurotoxicity at any dose level	WHO scale. Folstein mini-mental test at baseline, weekly during treatment and every 4 wk thereafter until progression.	CT or MRI of the brain 4 wk after treatment
	Huang et al., 2007	Seizures (grade III), muscle weakness (grade II) at 700 mg/m^2	CTC scale	MRI 1 mo after treatment, every 2 mo until progression or death. MMSE weekly during treatment, every 2 mo thereafter until progression.
Cisplatin	Stewart et al., 1982	Neurological deterioration and seizures (possibly due to other reasons than toxic effect)		Weekly blood counts. CT, audiography, and EEG as clinically needed.
Carboplatin	Guerrieri et al., 2004	Not suitable for evaluation because of poor accrual and early closure of trial. No difference between WBRT and WBRT + carboplatin group	Neurological function status	CT or MRI of brain 6 wk after treatment. WHO performance status, neurological function status, presence/absence of neurological symptoms.
Chemotherapy schedules				
Cisplatin, vinorelbine, ifosfamide	Quantin et al., 1999	Early dementia ($n = 1$)	Canadian Neurological Scale	Not described
	Quantin et al., 2010	No neurotoxicity reported	Neurological evaluation	Not described
Cisplatin, vindisine, mitomycine	Furuse et al., 1997	No neurotoxicity reported	WHO toxicity score	Weekly evaluation toxicity, neurological function classification by Borgelt, CT 8 wk after treatment and if neurological symptoms occurred
Pemetrexed, cisplatin or carboplatin	Chargari et al., 2013	Unexplained encephalopathy due to miliairy metastasis ($n = 1$), no increased neurotoxicity	CTCAE version 3.0	Gadolinium-enhanced MRI or contrast-enhanced CT 8 wk after treatment and if neurological symptoms occurred. Clinical examination, medical examination.
	Dinglin et al., 2013	Headache grade III ($n = 3$), nausea/vomiting grade III ($n = 8$)	NCI CTC version 2.0	Medical history and physical examination every 6 wk
Cisplatin, vinorelbine	Robinet et al., 2001	Confusion ($n = 1$), coma ($n = 2$), seizures ($n = 1$), worsening Parkinson's ($n = 1$)	WHO toxicity score	Not described

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Table 2. (continued)

Regimen	Author, year	Reported neurotoxicity	Method of evaluating toxicity	Follow-up toxicity characteristics
Cisplatin, etoposide	Chen et al., 2012	Grade III + IV nausea and vomiting (52.9%)	NCI CTC version 2.0	Medical history, physical examination, NCI CTC version 2.0
Cisplatin, paclitaxel with vinorelbine or gemcitabine	Cortes et al., 2003	Grade III neurotoxicity ($n = 1$)	WHO criteria	Physical examination, monitoring toxicity, CT
TKI				
Sunitinib	Chung et al., 2012	Grade I–II bleeding (unspecified location) and fatigue. No grade III or higher toxicity.	Not described	Not described
	Wuthrick et al., 2011	Grade I headache and motor neuropathy, grade III fatigue, dysphagia and difficulty chewing, grade II and V seizure (due to progression of brain metastasis)	CTCAE version 3.0	History, physical examinations, and hematology and chemistry studies weekly during treatment and 1 mo after treatment. MRI or CT 1 mo after treatment and at regular follow-up appointments.
Sunitinib and/or sorafenib	Arneson et al., 2014	No high-grade neurotoxicity	Not described	Not described
	Staehler et al., 2011	Asymptomatic grade II bleeding in tumor. Grade II convulsions. No grade III or higher neurotoxicity.	CTCAE version 3.0	CT and/or MRI every 12 wk
Erlotinib	Lind et al., 2009	Grade I–II headache. Grade I–III fatigue. No other neurotoxicity was reported.	CTCAE version 3.0	Toxicity assessment and clinical response at 1 wk and 2 wk of WBRT and at 2 wk, 4 wk, and 2 mo and then every 2 mo thereafter. MRI/CT at 3-mo intervals.
	Zhuang et al., 2013	No difference in toxicity between WBRT-only and WBRT + erlotinib groups. Grade I and II headache and dizziness.	CTCAE version 3.0	Whole-body examination at 1 mo and every 2–3 mo thereafter, including brain MRI, detailed medical history and physical examination
	Welsh et al., 2013	No difference in neurotoxicity compared with historical control group. Grade I–III headache and grade I–II dizziness was reported.	CTCAE version 3.0	Medical history, physical examination, neurological examination, MMSE, blood tests, toxicity evaluation at 1 mo and every 3 mo thereafter. MRI every 3 mo. Cognitive function (Hopkins Verbal Learning Test-Revised, Trail Making Test Parts A and B and Multilingual Aphasia Examination Controlled Oral Word Association test) every 3 mo
	Olmez et al., 2010	Mental status changes (category grade III–V), neurologic deterioration (category grade III–V)	NCI CTC version 3	–

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Table 2. (continued)

Regimen	Author, year	Reported neurotoxicity	Method of evaluating toxicity	Follow-up toxicity characteristics
	Cai et al., 2013	No significant difference between WBRT or WBRT + TKI. Headache, nausea, vomiting, and dizziness were reported, no grade was mentioned.	WHO anticancer drugs adverse reaction criteria and RTOG radioactive injury classification criteria	MRI after 1 mo
	Lee et al., 2014	No increase in neurotoxicity between RT + placebo or RT + erlotinib. Grade III or IV headache, muscle weakness, seizures, somnolence, and nausea were reported	CTCAE version 3.0	Adverse events were recorded up to 28 d after completion of erlotinib treatment
	Lee et al., 2012	No reported increase in neurotoxicity between RT-alone or RT + erlotinib groups. No specific neurotoxicity was reported.	CTCAE version 3.0	Not reported
	Sperduto et al., 2013	Significant increase in toxicity in RT + erlotinib group vs. RT alone. Muscle weakness, confusion (grade III), brain necrosis (grade IV), brain hemorrhage (gradeV)	CTCAE version 3.0	MRI, Functional Assessment of Cancer Treatment – General, performance status evaluation and steroid dose recording every 3 mo
Gefitinib	Wang et al., 2015	No reported neurotoxicity	CTCAE version 3.0	CT/MRI and clinical evaluation every 3 mo in first year and every 6 mo thereafter
	Zeng et al., 2012	Headache, vomiting, and hypomnesia were more common in WBRT + gefitinib group than WBRT-only group (not significant)	NCI CTC version 2.0	Monthly toxicity evaluations. MRI every 2-3 mo until progression
	Ma et al., 2009	Grade I–III nausea, vomiting, headache, and fatigue	NCI CTC	Weekly physical and neurological examinations during concurrent treatment
	Pesce et al., 2012	2 grade II fatigue, 2 grade III fatigue, and 1 grade IV fatigue. One case of grade III nausea/vomiting.	CTCAE version 3.0	Cognitive function measured with MMSE and Trailmaking Test Part B
Lapatinib	Lin et al., 2013	Grade I–II headache, neuropathy, dizziness, insomnia, memory impairment, depression, and weakness. One grade III or higher seizure, no other neurotoxicity of grade III or higher reported	CTCAE version 3.0	CT/MRI every 8 wk. Weekly clinical assessment during WBRT and at beginning of each cycle thereafter.
Vemurafenib	Schulze et al., 2014	Radiodermatitis	Not reported	Not reported
	Liebner et al., 2014	Symptomatic radionecrosis that required treatment	Not reported	Not reported

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Table 2. (continued)

Regimen	Author, year	Reported neurotoxicity	Method of evaluating toxicity	Follow-up toxicity characteristics
	Narayana et al., 2013	Radionecrosis that required steroid treatment	Not reported	Clinical observation every 4 wk. MRI at 6 wk and every 12 wk thereafter.
	Ahmed et al., 2015	Grade I headache. Seizure due to tumor recurrence and radiation necrosis. No grade III or greater toxicity reported.	RTOG grading system	Clinical examination and MRI every 2–3 mo
	Gaudy-Marqueste et al., 2014	Six neurological adverse events: confusion, paresthesia, hemiplegia, intracranial hypertension, convulsion on meningitis, and aphasia	Not reported	Clinical data, cerebral imaging follow-up
	Rompoti et al. 2013	No evidence of increased intracranial toxicity. Neurotoxicity was not specifically reported.	CTCAE version 4.02	MRI after 12 wk
Immunotherapy				
Ipilimumab	Silk et al., 2013	No increased neurotoxicity between RT alone and RT + ipilimumab. Intratumoral hemorrhage was reported.	Not mentioned	Unknown
	Mathew et al., 2013	No significant difference between SRS group and SRS + ipilimumab groups. Intratumoral hemorrhage was reported.	Not mentioned	Clinical investigation every 4 wk and MRI at 6 wk and every 12 wk thereafter
	Gerber et al., 2015	Possibly more intratumoral bleeding, grade III cognitive change. Otherwise low-grade neurotoxicity (headache, dizziness, fatigue, nausea, visual changes, cognitive changes, and seizures)	CTCAE version 4.0	Weekly assessment of neurological symptoms
	Tazi et al., 2015	Grade I–II hypopituitarism (1 case = 10%)	Unknown	
	Kiess et al., 2015	Grade III and IV CNS bleeding (from treated BM), grade III seizure. Otherwise low-grade neurotoxicity (headache, fatigue, cognitive changes, and neurological dysfunction)	CTCAE version 3.0	MRI 6-8 wk after SRS, then every 3 mo. Melanoma-specific graded prognostic assessment score.
Trastuzumab	Chargari et al., 2011	Headache, vertigo, and nausea (grade 1). No other neurotoxicity.	CTCAE version 3.0	MRI/CT 6 wk after treatment and in case of neurological symptoms. Clinical examination every 3 mo.

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Table 2. (continued)

Regimen	Author, year	Reported neurotoxicity	Method of evaluating toxicity	Follow-up toxicity characteristics
	Carlson et al., 2014	Increased symptomatic cerebral edema	Not reported	Not reported
Bevacizumab	Lèvy et al., 2014	Grade I–II headache, nausea, and vomiting. No grade III or higher toxicity.	CTCAE version 3.0	Recording of adverse events every week during treatment and at 3 mo after the treatment.

Abbreviations: BM, brain metastasis; CNS, central nervous system; CT, computed tomography; CTC, common toxicity criteria; CTCAE, Common Terminology Criteria for Adverse Event; EEG, electroencephalography; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NCI, National Cancer Institute; RT, radiotherapy; RTOG, Radiotherapy Oncology Group; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy; WHO, World Health Organization.

etoposide [28]. None of these trials reported high-grade neurotoxicity (Table 2).

One study described (Table 2) the concurrent use of carboplatin and cranial radiotherapy. This randomized phase III trial showed no significant increase in toxicity, whether carboplatin was added to WBRT or not. The pitfall of this trial was its early closing due to poor accrual. Because 43% of patients in the WBRT-alone arm and 14% in the combined-modality arm were not assessed for symptom control, no conclusion can be made concerning differences in neurotoxicity [29].

Taxanes: Paclitaxel/Docetaxel

Paclitaxel concurrently administered with WBRT and combined with cisplatin every 3 weeks is a feasible treatment schedule for patients with brain-metastasized NSCLC, without evidence for inducing significant neurotoxicity. This study did not score for QoL [30].

To our knowledge, no published clinical trials have administered docetaxel, alone or in a multiagent chemotherapy schedule, concurrently with cranial radiotherapy for the treatment of brain metastases.

Combination of Radiotherapy and Targeted Agents

Sunitinib and Sorafenib

Four studies described the toxicity (Table 2) of sunitinib (25 mg once daily or 37.5 mg once daily or 50 mg once daily for 4 weeks on, 2 weeks off) and/or sorafenib (400 mg once or twice daily) combined with cranial radiotherapy. Three studies described no grade III or higher neurotoxicity. Neurocognition and QoL were not assessed [31–33]. One study showed grade III fatigue and grade III dysphagia and drooling/difficulty chewing. One patient died of grade V seizures, but this was attributed to progression of brain metastasis. No testing was done regarding neurocognition or QoL [34].

Erlotinib

Eight studies with concurrent use of erlotinib (100 mg or 150 mg once daily) and cranial radiotherapy were identified (Table 2). One study reported no high-grade neurotoxicity [35]. Another study reported 1 case (out of 50) with grade III headache This study also evaluated neurocognition and found no statistical difference between the treatment group and a historical control group [36]. Four studies compared radiotherapy alone with radiotherapy combined with erlotinib. None of these trials reported a significant difference in neurotoxicity

between the treatment arms [37–40]. QoL was assessed in one study (EuroQol EQ-5D questionnaire), and no significant difference was observed between the treatment groups [37]. One retrospective study found grade III–V mental status changes in three cases without clear etiology. No other neurotoxicity was reported. Neurocognition and QoL were not assessed [41]. A phase III study compared the combination of WBRT and SRS with or without erlotinib. In the erlotinib group, grade III neurotoxicity, including fatigue, muscle weakness, confusion, and ataxia; grade IV brain necrosis; and one grade V hemorrhagic stroke were found. A significant increase in overall toxicity was found when erlotinib was added to cranial radiotherapy. QoL (by performance status) was also negatively affected by the addition of erlotinib to cranial radiotherapy [42].

Gefitinib

Five studies described toxicity (Table 2) when gefitinib (250 mg once daily) was combined with cranial radiotherapy. One study reported no neurotoxicity [43]; however, another study reported few cases of grade III neurotoxicity [44]. Both reported an improvement in QoL (activities of daily living scoring or Functional Assessment of Cancer Therapy-Brain [FACT-Br]) after treatment with gefitinib and cranial radiotherapy. One retrospective study reported slightly more headache, vomiting, and hypomnesia, although not significantly so, in the concurrent-use group compared with the gefitinib-only group. The performance score did not differ between the groups before or after treatment [45]. Another retrospective study compared toxicity between radiotherapy with or without gefitinib and found no difference in adverse events. Neurocognition and QoL were not assessed [39]. A phase II study reported different levels of fatigue. Grade III nausea and vomiting were also reported. Neurocognition and QoL (Folstein test, Trail-making Test part B, and Quality of Life Questionnaire-Core 36 score) were stable before and after the treatment period [46].

Lapatinib

One study described the toxicity (Table 2) of lapatinib (maximum, 1,500 mg once daily) combined with cranial radiotherapy. This trial reported a seizure in one patient. No other grade III or higher neurotoxicity was reported. QoL was scored by using FACT-Br and showed a general decline of QoL after the treatment. However, only a limited number of patients could be tested both at baseline and after finishing treatment [47].
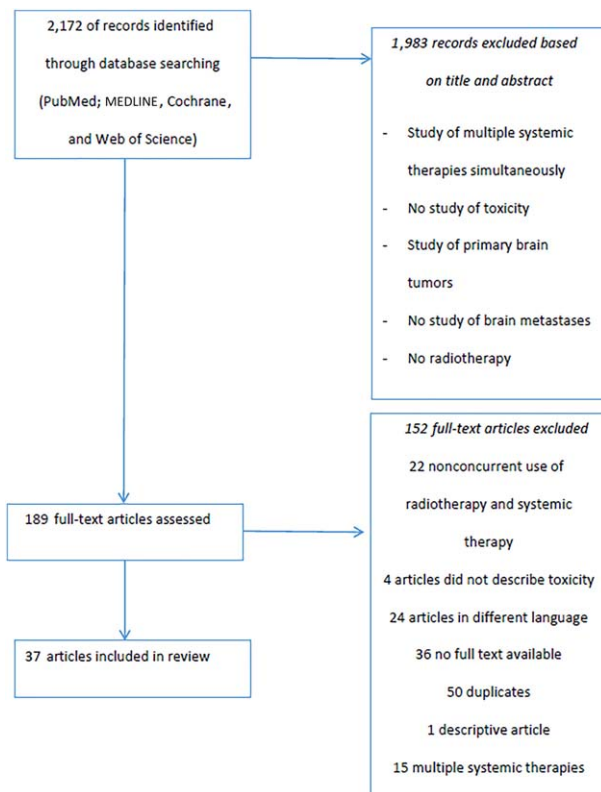
Figure 1. Selection process of literature search.

Vemurafenib

Six papers described toxicity (Table 2) with the concurrent use of vemurafenib (960 mg twice daily) and cranial radiotherapy. Two case reports of patients with brain metastases of melanoma reported radiation dermatitis on the radiated site [48]. Two other case reports of patients with brain metastases of melanoma reported symptomatic radionecrosis; however, neurotoxicity was not scored [49]. A retrospective study also identified symptoms due to radionecrosis in 1 of 12 patients [50]. Another retrospective study reported 1 melanoma patient with brain metastases who developed a seizure. However, it was not clear whether the seizure was caused by tumor progression or by radiation necrosis. No (other) significant toxicity was reported [51]. A third retrospective study reported the following symptoms in 6 melanoma patients with brain metastases: confusion, paresthesia, hemiplegia, intracranial hypertension, convulsion on meningitis, and aphasia. No grading system was used to assess the severity. All these patients had highly metastatic (4–20 brain metastases) cerebral disease [52]. Additionally, 4 case reports in patients with brain metastases from melanoma described no evidence of increased intracranial toxicity with concurrent use of WBRT and vemurafenib [53]. None of these studies assessed neurocognition or QoL.

Combination of Radiotherapy and Monoclonal Antibodies

Immune Checkpoint Inhibitors: Ipilimumab

Five articles describe toxicity (Table 2) when ipilimumab (3 or 10 mg/kg every 3 weeks) was combined with cranial radiotherapy. One study reported no high-grade neurotoxicity, and QoL (performance status) did not change for 8 of 10 patients [54]. Two studies compared a radiotherapy-only group with a radiotherapy plus ipilimumab group and reported no difference in

toxicity [55, 56]. One retrospective study described possibly more intratumoral bleeding with administration of ipilimumab concurrently with radiotherapy. However, this did not require any intervention. This trial also described one patient with grade III cognitive impairment during WBRT. Other reported neurotoxicity was only low grade. QoL was not assessed [57]. Another retrospective study described grade III–IV toxicity in 20% of melanoma patients treated with radiation therapy combined with ipilimumab, including both neurological and non-neurological toxicity. Neurological toxicity included bleeding from treated brain metastasis (grade III and IV) and seizures (grade III). QoL was not assessed [58].

Trastuzumab

Two studies reported the toxicity (Table 2) of the combination of trastuzumab (2 mg/kg weekly or 6 mg/kg every 3 weeks) and cranial radiotherapy. One retrospective study reported no high-grade neurotoxicity. QoL was not scored [59]. Another article reported four case reports in which multiple neurological symptoms (headache, nausea/vomiting, speech impairment, short-term memory deficits, imbalance, gait disturbance, and visual deficits) were observed, all of which were attributed to brain edema due to concurrent use of trastuzumab and cranial radiotherapy. The level of neurotoxicity was not scored [60].

Bevacizumab

One study evaluated toxicity (Table 2) for the concurrent use of bevacizumab (15 mg/kg three times a month) and cranial radiotherapy for brain metastases. This phase I study reported no high-grade neurotoxicity and did not assess neurocognition and QoL [61].

DISCUSSION

Approximately 10%–20% of all solid tumors will eventually metastasize to the brain. NSCLC, small cell lung cancer, breast cancer, melanoma, and RCC are the most common primary tumors that develop brain metastases [8]. Cranial radiotherapy is still the standard treatment of symptomatic brain metastases. There is growing evidence that some systemic anticancer agents may also control brain metastases in selected patients, especially when brain metastases are asymptomatic and relatively small [2]. When brain metastases progress and become symptomatic and unresponsive to the systemic anticancer treatment that is administered to control the extracerebral metastases, a repeated question is whether the systemic treatment should be discontinued at the time of cranial radiotherapy of brain metastases in order to prevent significant neurotoxicity. Instead of long-term discontinuation, a more pragmatic approach can be defended, for example, discontinuation 1 week before to 1 week after the cranial radiotherapy. This approach seemed to be feasible on the basis of the data from a recently published retrospective study, which combined SRS with multiple types of systemic anticancer therapies, without increasing neurotoxicity. However, no information on issues such as treatment schedule and drug dosage was provided [62].

It is obvious that multiple factors should be taken into account in addressing whether to discontinue systemic therapies during cranial radiotherapy. One of these factors is a significant interpatient and intrapatient variation in the intratumoral

concentration of specific oncolytics in brain metastases due to differences in permeability of the blood-tumor-barrier (BTB) for different anticancer agents and also in the expression of drug efflux pumps, such as P-glycoprotein [63–66]. Table 1 shows these pharmacological characteristics for the different anticancer agents.

The trials described in this article do not show increased neurotoxicity for capecitabine, 5-fluoroucil (5-FU), cisplatin and carboplatin, or taxanes when administered concurrently with cranial radiotherapy. This is the case for both monotherapy and also combined in multidrug schedules, commonly used in the palliative treatment of metastasized solid tumors (Table 2). However, it should be taken into account that high-level evidence is lacking. Moreover, data regarding neurocognitive impairment and decreases in QoL are extremely sparse because most studies are retrospective or did not include these data. Also, the methods used to assess neurocognition (e.g., Folstein test) are insensitive and therefore cannot secure a lack of neurocognitive toxicity [67]. On the basis of the available information the chemotherapy regimens containing 5-FU or capecitabine could be continued, when symptomatic brain metastases require treatment with cranial radiotherapy, and only when extracerebral tumor load necessitates protracted systemic treatment.

Combining gemcitabine, at a dose of 700 mg/m^2, with cranial radiotherapy is not feasible because of a significant increase in neurotoxicity [17]. It is expected that the commonly used schedule of administrating gemcitabine at a dose of 1,000 mg/m^2 will result in clinically significant neurotoxicity when used concurrently with WBRT. The $t_{1/2}$ of gemcitabine is short: 0.7–1.6 hours (Table 1). It is expected that 97% of this drug is eliminated after 8 hours (5 times $t_{1/2}$). Because gemcitabine is also metabolized into active metabolites intra-tumorally, neurotoxicity can still occur when cranial radiotherapy is started after complete drug elimination is reached. There are no data available that define when cranial radiotherapy can be safely started after discontinuing gemcitabine; gemcitabine-induced radiation recall has been described from 3 weeks to 8 months from the time gemcitabine was initiated. According to the available literature, which is sparse and might underestimate the risk for increased neurotoxicity, the concurrent and sequential use of gemcitabine and cranial radiotherapy should be discouraged.

Inhibitors of angiogenesis (e.g., sunitinib and sorafenib) are routinely used to treat metastasized RCC [68]. For patients with symptomatic brain metastases of RCC, combination with cranial radiotherapy did not result in clinically significant neurotoxicity. However, clinical trials included only a small number of patients, and both neurocognitive testing and scoring of QoL were limited. Again, high-level evidence is lacking. Because these drugs are known to be radiosensitizing, one should be reluctant to combine these multi-tyrosine kinase inhibitors with cranial radiotherapy.

It is not clear how long these targeted agents should be discontinued before cranial radiotherapy begins in order to sufficiently abolish their metabolic activity. On the basis of $t_{1/2}$ of these molecules and their active metabolites, sunitinib should be stopped at least for 550 hours (5 times $t_{1/2}$) and sorafenib for 240 hours (5 times $t_{1/2}$) to achieve 97% excretion before radiation therapy is started (Table 1) [69, 70]. During this long period of discontinuation, flare of tumor activity of

extracerebral metastases might occur. In addition, it is important to realize that even after complete excretion, the metabolic activity of these agents in brain metastases might still be ongoing; it has not been established that 5 times $t_{1/2}$ or 97% excretion is directly correlated to the metabolic activity of these drugs.

Concerning the risk for intratumoral bleeding, a database search of clinical trials that included patients with or without central nervous system (CNS) metastases and treated with sunitinib, sorafenib, or bevacizumab did not show an increased risk for cerebral hemorrhage. The safety of bevacizumab with regard to cerebral hemorrhage in patients with CNS metastasis of breast cancer, NSCLC, RCC, and colorectal cancer was also described and confirmed in a large retrospective analysis [71, 72].

Gefitinib was not shown to cause increased neurotoxicity or a deterioration of neurocognition and QoL when combined with cranial radiotherapy, although the tests used to measure neurocognition and QoL were insensitive and therefore not conclusive. Concurrent use of erlotinib, another tyrosine-kinase inhibitor of endothelial growth factor receptor, was associated with significant neurotoxicity when both WBRT and SRS were used [42]. Although high-level evidence is lacking, this combination should be discouraged. The safety of cranial radiotherapy combined with TKIs, used in NSCLC, was recently reviewed by Hendriks et al. [73].

> Gefitinib was not shown to cause increased neurotoxicity or a deterioration of neurocognition and QoL when combined with cranial radiotherapy, although the tests used to measure neurocognition and QoL were insensitive and therefore not conclusive.

An incidental increase in neurotoxicity has also been reported when other tyrosine kinase inhibitors, such as vemurafenib, are combined with cranial radiotherapy. This is supported by a statement from the manufacturer, in agreement with the European Medicines Agency, which advises caution when vemurafenib is used before, during, or after cranial radiotherapy [74]. A recently published literature review on the combination of BRAF inhibitors and cranial radiotherapy recommends holding BRAF inhibitors for at least 3 days before and after fractional radiotherapy and at least 1 day before and after stereotactic radiosurgery [75].

However, the duration of discontinuation of systemic oncolytics remains a matter of debate.

Ninety-seven percent plasma elimination of these drugs is achieved after 5 times $t_{1/2}$. However, this does not include any remaining metabolic activities of these tyrosine kinase inhibitors intratumorally, as mentioned earlier. Thus, increased neurotoxicity with neurocognitive deterioration and decreased QoL can never be completely prevented, especially because it is not known whether there is a dose-dependent effect for radiosensitization. Therefore, the risks for extracerebral tumor flare after stopping TKI should be weighed against the risks for increased neurotoxicity due to concurrent treatment.

Immune checkpoint modulators, such as ipilimumab, a large monoclonal antibody, are unable to penetrate the BBB in patients without brain metastases (Table 1) [76]. However, in brain metastases the BBB is mostly disrupted, which may facilitate ipilimumab to cross the perivascular space and activate peripherally recruited T cells. Alternatively, ipilimumab-activated T cells in the peripheral circulation may enter the brain metastases through the BBB/BTB. Combining radiation therapy for melanoma brain metastases with ipilimumab appears to be safe and well tolerated. However, a mostly asymptomatic, transient increase of lesion size, suggesting subacute inflammatory response or intratumoral bleeding, was seen in several studies in which SRS was combined with ipilimumab. This pseudoprogression was not present when SRS was given after completion of ipilimumab treatment [58].

Further studies are needed to investigate the ideal sequence of ipilimumab and SRS in order to minimize side effects while maximizing efficacy. Research is also ongoing on whether SRS before or during ipilimumab and potentially other immune checkpoint modulators might increase the immune response by increasing the release of tumor antigens. In addition, one could anticipate an effect on nonirradiated lesions and ultimately the prevention of new metastatic events, the so-called abscopal effect [77, 78].

Other monoclonal antibodies, such as trastuzumab, are also very limited in passing the intact BBB because of their large molecular weight (Table 1). However, trastuzumab can prolong median overall survival in patients with brain metastasized HER2-expressing breast tumors, suggesting its permeation through the BTB [79, 80]. When brain metastases develop during trastuzumab treatment, combination with radiation therapy seems to be safe and feasible.

Conclusion

Brain metastases may develop during systemic treatment schedules that successfully control extracerebral tumor metastases. Cranial radiotherapy is traditionally used to control symptomatic brain metastases. Among all the systemic cancer treatments reviewed, an elevated risk for neurotoxicity was described with gemcitabine, erlotinib, and vemurafenib.

However, caution should be used in interpreting these results because most studies are retrospective studies or small phase I trials that performed only limited screening for neurotoxicity. Therefore, no definite conclusions can be made regarding the concurrent use of these oncolytics with cranial radiotherapy on the basis of the data currently available. However, there is growing evidence that not all systemic therapies need to be discontinued during cranial radiotherapy. Prospective randomized trials with overall survival as well as neurocognition and QoL as endpoints are needed in this palliative patient subset. Immune checkpoint modulators and treatments that activate the immune system are promising. They are being investigated with regard to whether their combination with cranial radiotherapy may improve treatment outcome in the setting of brain metastases to induce an abscopal effect.

References

1. Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. J Clin Oncol 2005;23:6207–6219.

2. Lin X, DeAngelis LM. Treatment of brain metastases. J Clin Oncol 2015;33:3475–3484.

3. Dy GK, Adjei AA. Systemic cancer therapy: Evolution over the last 60 years. Cancer 2008;113:1857–1887.

4. Jordan VC, Brodie AM. Development and evolution of therapies targeted to the estrogen receptor for the treatment and prevention of breast cancer. Steroids 2007;72:7–25.

5. Segal NH, Saltz LB. Evolving treatment of advanced colon cancer. Annu Rev Med 2009;60:207–219.

6. Colozza M, de Azambuja E, Cardoso F et al. Breast cancer: Achievements in adjuvant systemic therapies in the pre-genomic era. *The Oncologist* 2006;11:111–125.

7. Salama JK, Milano MT. Radical irradiation of extracranial oligometastases. J Clin Oncol 2014;32:2902–2912.

8. Nussbaum ES, Djalilian HR, Cho KH et al. Brain metastases. Histology, multiplicity, surgery, and survival. Cancer 1996;78:1781–1788.

9. Dzienis MR, Atkinson VG. Response rate to vemurafenib in patients with B-RAF-positive melanoma brain metastases: A retrospective review. Melanoma Res 2014;24:349–353.

10. Fan Y, Xu X, Xie C. EGFR-TKI therapy for patients with brain metastases from non-small-cell lung cancer: A pooled analysis of published data. Onco Targets Ther 2014;7:2075–2084.

11. Peters NA, Richel DJ, Verhoeff JJ et al. Bowel perforation after radiotherapy in a patient receiving sorafenib. J Clin Oncol 2008;26:2405–2406.

12. Inoue T, Kinoshita H, Komai Y et al. Two cases of gastrointestinal perforation after radiotherapy in patients receiving tyrosine kinase inhibitor for advanced renal cell carcinoma. World J Surg Oncol 2012;10:167.

13. Zhuang H, Yuan Z, Chang JY et al. Radiation pneumonitis in patients with non–small-cell lung cancer treated with erlotinib concurrent with thoracic radiotherapy. J Thorac Oncol 2014;9:882–885.

14. Chargari C, Kirova YM, Dieras V et al. Concurrent capecitabine and whole-brain radiotherapy for treatment of brain metastases in breast cancer patients. J Neurooncol 2009;93:379–384.

15. Niravath P, Tham YL, Wang T et al. A phase II trial of capecitabine concomitantly with whole-brain radiotherapy followed by capecitabine and sunitinib for brain metastases from breast cancer. *The Oncologist* 2015;20:13.

16. Maraveyas A, Sgouros J, Upadhyay S et al. Gemcitabine twice weekly as a radiosensitiser for the treatment of brain metastases in patients with carcinoma: A phase I study. Br J Cancer 2005;92:815–819.

17. Huang YJ, Wu YL, Xie SX, et al. Weekly gemcitabine as a radiosensitiser for the treatment of brain metastases in patients with non-small cell lung cancer: Phase I trial. Chin Med J (Engl) 2007;120:458–462.

CME

18. Schwarte S, Wagner K, Karstens JH et al. Radiation recall pneumonitis induced by gemcitabine. Strahlenther Onkol 2007;183:215–217.

19. Schwartz BM, Khuntia D, Kennedy AW et al. Gemcitabine-induced radiation recall dermatitis following whole pelvic radiation therapy. Gynecol Oncol 2003;91:421–422.

20. Jeter MD, Janne PA, Brooks S et al. Gemcitabine-induced radiation recall. Int J Radiat Oncol Biol Phys 2002;53:394–400.

21. Stewart DJ, Leavens M, Maor M et al. Human central nervous system distribution of cis-diamminedichloroplatinum and use as a radiosensitizer in malignant brain tumors. Cancer Res 1982;42:2474–2479.

22. Quantin X, Khial F, Reme-Saumon M et al. Concomitant brain radiotherapy and vinorelbine-ifosfamide-cisplatin chemotherapy in brain metastases of non-small cell lung cancer. Lung Cancer 1999;26:35–39.

23. Quantin X, Bozonnat MC, Pujol JL. Recursive partitioning analysis groups II-III brain metastases of non-small cell lung cancer: A phase II randomized study comparing two concurrent chemoradiotherapy regimens. J Thorac Oncol 2010;5:846–851.

24. Furuse K, Kamimori T, Kawahara M et al. A pilot study of concurrent whole-brain radiotherapy and chemotherapy combined with cisplatin, vindesine and mitomycin in non-small-cell lung cancer with brain metastasis. Br J Cancer 1997;75:614–618.

25. Dinglin XX, Huang Y, Liu H et al. Pemetrexed and cisplatin combination with concurrent whole brain radiotherapy in patients with brain metastases of lung adenocarcinoma: A single-arm phase II clinical trial. J Neurooncol 2013;112:461–466.

26. Chargari C, Pacaut C, Le Moulec S et al. First assessment of whole-brain radiation therapy combined with pemetrexed-based chemotherapy in non-small-cell lung carcinoma: Data on safety and efficacy. Anticancer Drugs 2013;24:736–742.

27. Robinet G, Thomas P, Breton JL et al. Results of a phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in inoperable brain metastasis of non-small-cell lung cancer: Groupe Francais de Pneumo-cancerologie (GFPC) protocol 95–1. Ann Oncol 2001;12:59–67.

28. Chen LK, Huang H, Liao H et al. Chemotherapy with concurrent brain and thoracic radiotherapy in brain-only metastases of treatment naive small-cell lung cancer: A phase II study. Med Oncol 2012;29:1687–1692.

29. Guerrieri M, Wong K, Ryan G et al. A randomised phase III study of palliative radiation with concomitant carboplatin for brain metastases from non-small cell carcinoma of the lung. Lung Cancer 2004;46:107–111.

30. Arrieta O, Villarreal-Garza C, Zamora J et al. Long-term survival in patients with non-small cell lung cancer and synchronous brain metastasis treated with whole-brain radiotherapy and thoracic chemoradiation. Radiat Oncol 2011;6:166.

31. Staehler M, Haseke N, Nuhn P et al. Simultaneous anti-angiogenic therapy and single-fraction radiosurgery in clinically relevant metastases from renal cell carcinoma. BJU Int 2011;108:673–678.

32. Arneson K, Mondshein J, Cmelak AJ et al. A phase 1 trial of concurrent sorafenib and stereotactic radiosurgery for patients with 1–4 brain metastases. Int J Radiat Oncol Biol Phys 2014;87:S271.

33. Chung C, Menard C, Stevens C et al. Phase I dose escalation study of sunitinib and radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys 2012;84(Suppl 12):S77.

34. Wuthrick EJ, Kamrava M, Curran WJ Jr. et al. A phase 1b trial of the combination of the antiangiogenic agent sunitinib and radiation therapy for patients with primary and metastatic central nervous system malignancies. Cancer 2011;117:5548–5559.

35. Lind JS, Lagerwaard FJ, Smit EF et al. Phase I study of concurrent whole brain radiotherapy and erlotinib for multiple brain metastases from non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2009;74:1391–1396.

36. Welsh JW, Komaki R, Amini A et al. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. J Clin Oncol 2013;31:895–902.

37. Lee SM, Lewanski CR, Counsell N et al. Randomized trial of erlotinib plus whole-brain radiotherapy for NSCLC patients with multiple brain metastases. J Natl Cancer Inst 2014;106

38. Lee HL, Chung TS, Ting LL et al. EGFR mutations are associated with favorable intracranial response and progression-free survival following brain irradiation in non-small cell lung cancer patients with brain metastases. Radiat Oncol 2012;7:181.

39. Cai Y, Wang JY, Liu H. Clinical observation of whole brain radiotherapy concomitant with targeted therapy for brain metastasis in non-small cell lung cancer patients with chemotherapy failure. Asian Pac J Cancer Prev 2013;14:5699–5703.

40. Zhuang H, Yuan Z, Wang J et al. Phase II study of whole brain radiotherapy with or without erlotinib in patients with multiple brain metastases from lung adenocarcinoma. Drug Des Devel Ther 2013;7:1179–1186.

41. Olmez I, Donahue BR, Butler JS et al. Clinical outcomes in extracranial tumor sites and unusual toxicities with concurrent whole brain radiation (WBRT) and erlotinib treatment in patients with non-small cell lung cancer (NSCLC) with brain metastasis. Lung Cancer 2010;70:174–179.

42. Sperduto PW, Wang M, Robins HI et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. Int J Radiat Oncol Biol Phys 2013;85:1312–1318.

43. Wang F, Ning F, Liu C et al. Comparison of gefitinib versus VMP in the combination with radiotherapy for multiple brain metastases from non-small cell lung cancer. Cell Biochem Biophys 2015;71:1261–1265.

44. Ma S, Xu Y, Deng Q et al. Treatment of brain metastasis from non-small cell lung cancer with whole brain radiotherapy and gefitinib in a Chinese population. Lung Cancer 2009;65:198–203.

45. Zeng YD, Zhang L, Liao H et al. Gefitinib alone or with concomitant whole brain radiotherapy for patients with brain metastasis from non-small-cell lung cancer: A retrospective study. Asian Pacif J Cancer Prev 2012;13:909–914.

46. Pesce GA, Klingbiel D, Ribi K et al. Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the Swiss Group for Clinical Cancer Research (SAKK 70/03). Eur J Cancer 2012;48:377–384.

47. Lin NU, Freedman RA, Ramakrishna N et al. A phase I study of lapatinib with whole brain radiotherapy in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer brain metastases. Breast Cancer Res Treat 2013;142:405–414.

48. Schulze B, Meissner M, Wolter M et al. Unusual acute and delayed skin reactions during and after whole-brain radiotherapy in combination with the braf inhibitor vemurafenib. Two case reports. Strahlenther Onkol 2014;190:229–232.

49. Liebner DA, Walston SA, Cavaliere R et al. Radiation necrosis mimicking rapid intracranial progression of melanoma metastasis in two patients treated with vemurafenib. Melanoma Res 2014;24:172–176.

50. Narayana A, Mathew M, Tam M et al. Vemurafenib and radiation therapy in melanoma brain metastases. J Neurooncol 2013;113:411–416.

51. Ahmed KA, Freilich JM, Sloot S et al. Linac-based stereotactic radiosurgery to the brain with concurrent vemurafenib for melanoma metastases. J Neurooncol 2015;122:121–126.

52. Gaudy-Marqueste C, Carron R, Delsanti C et al. On demand gamma-knife strategy can be safely combined with BRAF inhibitors for the treatment of melanoma brain metastases. Ann Oncol 2014;25:2086–2091.

53. Rompoti N, Schilling B, Livingstone E et al. Combination of BRAF inhibitors and brain radiotherapy in patients with metastatic melanoma shows minimal acute toxicity. J Clin Oncol 2013;31:3844–3845.

54. Tazi K, Hathaway A, Chiuzan C et al. Survival of melanoma patients with brain metastases treated with ipilimumab and stereotactic radiosurgery. Cancer Med 2015;4:1–6.

55. Mathew M, Tam M, Ott PA et al. Ipilimumab in melanoma with limited brain metastases treated with stereotactic radiosurgery. Melanoma Res 2013;23:191–195.

56. Silk AW, Bassetti MF, West BT et al. Ipilimumab and radiation therapy for melanoma brain metastases. Cancer Med 2013;2:899–906.

57. Gerber NK, Young RJ, Barker CA et al. Ipilimumab and whole brain radiation therapy for melanoma brain metastases. J Neurooncol 2015;121:159–165.

58. Kiess AP, Wolchok JD, Barker CA et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: Safety profile and efficacy of combined treatment. Int J Radiat Oncol Biol Phys 2015;92:368–375.

59. Chargari C, Idrissi HR, Pierga JY et al. Preliminary results of whole brain radiotherapy with concurrent trastuzumab for treatment of brain metastases in breast cancer patients. Int J Radiat Oncol Biol Phys 2011;81:631–636.

60. Carlson JA, Nooruddin Z, Rusthoven C et al. Trastuzumab emtansine and stereotactic radiosurgery: An unexpected increase in clinically significant brain edema. Neurooncology 2014;16:1006–1009.

61. Lèvy C, Allouache D, Lacroix J et al. REBECA: A phase I study of bevacizumab and whole-brain radiation therapy for the treatment of brain metastasis from solid tumours. Ann Oncol 2014;25:2351–2356.

62. Shen CJ, Kummerlowe MN, Redmond KJ et al. Stereotactic radiosurgery: Treatment of brain metastasis without interruption of systemic therapy. Int J Radiat Oncol Biol Phys 2016;95:735–742.

63. Cordon-Cardo C, O'Brien JP, Boccia J et al. Expression of the multidrug resistance gene product

CME

(p-glycoprotein) in human normal and tumor tissues. J Histochem Cytochem 1990;38:1277–1287.

64. Demeule M, Shedid D, Beaulieu E et al. Expression of multidrug-resistance p-glycoprotein (MDR1) in human brain tumors. Int J Cancer 2001;93:62–66.

65. Regina A, Demeule M, Laplante A et al. Multidrug resistance in brain tumors: Roles of the blood-brain barrier. Cancer Metastasis Rev 2001;20:13–25.

66. Lockman PR, Mittapalli RK, Taskar KS et al. Heterogeneous blood-tumor barrier permeability determines drug efficacy in experimental brain metastases of breast cancer. Clin Cancer Res 2010;16:5664–5678.

67. Meyers CA, Wefel JS. The use of the Mini-Mental State Examination to assess cognitive functioning in cancer trials: No ifs, ands, buts, or sensitivity. J Clin Oncol 2003;21:3557–3558.

68. Berghoff AS, Ilhan-Mutlu A, Dinhof C et al. Differential role of angiogenesis and tumour cell proliferation in brain metastases according to primary tumour type: Analysis of 639 cases. Neuropathol Appl Neurobiol 2015;41:e41–55.

69. Caffo M, Barresi V, Caruso G et al. Innovative therapeutic strategies in the treatment of brain metastases. Int J Mol Sci 2013;14:2135–2174.

70. Kim A, McCully C, Cruz R et al. The plasma and cerebrospinal fluid pharmacokinetics of sorafenib after intravenous administration in non-human primates. Invest New Drugs 2012;30:524–528.

71. Besse B, Lasserre SF, Compton P et al. Bevacizumab safety in patients with central nervous system metastases. Clin Cancer Res 2010;16:269–278.

72. Carden CP, Larkin JM, Rosenthal MA. What is the risk of intracranial bleeding during anti-vegf therapy? Neurooncology 2008;10:624–630.

73. Hendriks LE, Schoenmaekers J, Zindler JD et al. Safety of cranial radiotherapy concurrent with tyrosine kinase inhibitors in non-small cell lung cancer patients: A systematic review. Cancer Treat Rev 2015;41:634–645.

74. Roche Products Ltd. Potentiation of radiation toxicity associated with zelboraf (vemurafenib). Letter to Healthcare Workers. 2015.

75. Anker CJ, Grossmann KF, Atkins MB et al. Avoiding severe toxicity from combined BRAF inhibitor and radiation treatment: Consensus guidelines from the Eastern Cooperative Oncology Group (ECOG). Int J Radiat Oncol Biol Phys 2016;95:632–646.

76. Carson MJ, Doose JM, Melchior B et al. CNS immune privilege: Hiding in plain sight. Immunol Rev 2006;213:48–65.

77. Rodel F, Frey B, Multhoff G et al. Contribution of the immune system to bystander and non-targeted effects of ionizing radiation. Cancer Lett 2015;356:105–113.

78. Stamell EF, Wolchok JD, Gnjatic S et al. The abscopal effect associated with a systemic anti-melanoma immune response. Int J Radiat Oncol Biol Phys 2013;85:293–295.

79. Park YH, Park MJ, Ji SH et al. Trastuzumab treatment improves brain metastasis outcomes through control and durable prolongation of systemic extracranial disease in HER2-overexpressing breast cancer patients. Br J Cancer 2009;100:894–900.

80. Park IH, Ro J, Lee KS et al. Trastuzumab treatment beyond brain progression in HER2-positive metastatic breast cancer. Ann Oncol 2009;20:56–62.

81. Twelves C, Glynne-Jones R, Cassidy J et al. Effect of hepatic dysfunction due to liver metastases on the pharmacokinetics of capecitabine and its metabolites. Clin Cancer Res 1999;5:1696–1702.

82. Judson IR, Beale PJ, Trigo JM et al. A human capecitabine excretion balance and pharmacokinetic study after administration of a single oral dose of 14c-labelled drug. Invest New Drugs 1999;17:49–56.

83. European Medicines Agency. European public assessment reports 2015. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0-b01ac058001d124. Accessed May 29, 2015.

84. Morikawa A, Peereboom DM, Thorsheim HR et al. Capecitabine and lapatinib uptake in surgically resected brain metastases from metastatic breast cancer patients: A prospective study. Neurooncology 2015;17:289–295.

85. van der Vijgh WJ. Clinical pharmacokinetics of carboplatin. Clin Pharmacokinet 1991;21:242–261.

86. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. J Clin Oncol 1999;17:409–422.

87. Pitz MW, Desai A, Grossman SA et al. Tissue concentration of systemically administered antineoplastic agents in human brain tumors. J Neurooncol 2011;104:629–638.

88. ten Tije AJ, Loos WJ, Zhao M et al. Limited cerebrospinal fluid penetration of docetaxel. Anticancer Drugs 2004;15:715–718.

89. Heimans JJ, Vermorken JB, Wolbers JG et al. Paclitaxel (Taxol) concentrations in brain tumor tissue. Ann Oncol 1994;5:951–953.

90. Fine RL, Chen J, Balmaceda C et al. Randomized study of paclitaxel and tamoxifen deposition into human brain tumors: Implications for the treatment of metastatic brain tumors. Clin Cancer Res 2006;12:5770–5776.

91. Deng Y, Feng W, Wu J et al. The concentration of erlotinib in the cerebrospinal fluid of patients with brain metastasis from non-small-cell lung cancer. Mol Clin Oncol 2014;2:116–120.

92. Togashi Y, Masago K, Masuda S et al. Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer. Cancer Chemother Pharmacol 2012;70:399–405.

93. Yang H, Yang X, Zhang Y et al. Erlotinib in combination with pemetrexed/cisplatin for leptomeningeal metastases and cerebrospinal fluid drug concentrations in lung adenocarcinoma patients after gefitinib failure. Target Oncol 2015;10:135–140.

94. Clarke JL, Pao W, Wu N et al. High dose weekly erlotinib achieves therapeutic concentrations in CSF and is effective in leptomeningeal metastases from epidermal growth factor receptor mutant lung cancer. J Neurooncol 2010;99:283–286.

95. Raizer JJ, Abrey LE, Lassman AB et al. A phase II trial of erlotinib in patients with recurrent malignant gliomas and nonprogressive glioblastoma multiforme postradiation therapy. Neurooncology 2010; 12:95–103.

96. Zhao J, Chen M, Zhong W et al. Cerebrospinal fluid concentrations of gefitinib in patients with lung adenocarcinoma. Clin Lung Cancer 2013;14:188–193.

97. Hofer S, Frei K. Gefitinib concentrations in human glioblastoma tissue. J Neurooncol 2007;82: 175–176.

98. Polli JW, Humphreys JE, Harmon KA et al. The role of efflux and uptake transporters in [n-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine (gw572016, lapatinib) disposition and drug interactions. Drug Metab Dispos 2008;36:695–701.

99. Sakji-Dupre L, Le Rhun E, Templier C et al. Cerebrospinal fluid concentrations of vemurafenib in patients treated for brain metastatic braf-v600 mutated melanoma. Melanoma Res 2015;25:302–305.

100. Lee JM, Mehta UN, Dsouza LH et al. Long-term stabilization of leptomeningeal disease with whole-brain radiation therapy in a patient with metastatic melanoma treated with vemurafenib: A case report. Melanoma Res 2013;23:175–178.

101. Mittapalli RK, Vaidhyanathan S, Sane R et al. Impact of p-glycoprotein (abcb1) and breast cancer resistance protein (abcg2) on the brain distribution of a novel BRAF inhibitor: Vemurafenib (plx4032). J Pharmacol Exp Ther 2012;342:33–40.

102. Bartsch R, Rottenfusser A, Wenzel C et al. Trastuzumab prolongs overall survival in patients with brain metastases from her2 positive breast cancer. J Neurooncol 2007;85:311–317.

103. Yoshida Y, Hoshino S, Aisu N et al. Efficacy of XELOX plus bevacizumab in brain metastasis from rectal cancer. Case Rep Oncol 2014;7:117–121.

104. Ay I, Francis JW, Brown RH, Jr. VEGF increases blood-brain barrier permeability to evans blue dye and tetanus toxin fragment C but not adeno-associated virus in ALS mice. Brain Res 2008;1234: 198–205.

105. Caffo M, Barresi V, Caruso G et al. Innovative therapeutic strategies in the treatment of brain metastases. Int J Molec Sci 2013;14:2135–2174.

106. Kim A, McCully C, Cruz R et al. The plasma and cerebrospinal fluid pharmacokinetics of sorafenib after intravenous administration in non-human primates. Invest New Drugs 2012;30:524–528.

107. Mehta AI, Brufsky AM, Sampson JH. Therapeutic approaches for HER2-positive brain metastases: Circumventing the blood-brain barrier. Cancer Treat Rev 2013;39:261–269.

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