Targeted Therapy for Brain Metastases: Improving the Therapeutic Ratio

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Abstract   Brain metastasis is the most common intracranial malignancy in adults. Improvements in modern imaging techniques are detecting previously occult brain metastases, and more effective therapies are extending the survival of patients with invasive cancer who have historically died from extracranial disease before developing brain metastasis. This combination of factors along with increased life expectancy has led to the increased diagnosis of brain metastases. Conventional treatment has been whole brain radiotherapy, which can improve symptoms, but potentially results in neurocognitive deficits. Several strategies to improve the therapeutic ratio are currently under investigation to either enhance the radiation effect, thereby preventing tumor recurrence or progression as well as reducing collateral treatment-related brain injury. In this review article, we discuss new directions in the management of brain metastases, including the role of chemical modifiers, novel systemic agents, and the management and prevention of neurocognitive deficits.

Brain metastases represent an important cause of morbidity and mortality and are the most common intracranial tumors in adults, occurring in ∼ 10% to 30% of adult cancer patients (1). It is speculated that the annual incidence is increasing for several reasons, including an aging population, better treatment of systemic disease, and the improved ability of imaging modalities, such as magnetic resonance imaging, to detect smaller metastases in asymptomatic patients (1). Improved systemic therapy is directly contributing to an increased incidence of brain metastases, especially in patients with breast cancer, whereby improved cytotoxic and novel targeted therapies such as trastuzumab allow patients to survive much longer than before (2). The risk of developing brain metastases varies according to primary tumor type, with lung cancer accounting for approximately one half of all brain metastases (3). Other malignancies commonly associated with brain metastases are breast cancer (15-20%), unknown primary (10-15%), and melanoma (10-15%). Brain metastases may be single, few, or several. Melanoma and lung cancer are frequently associated with multiple metastases whereas solitary metastases are more commonly seen in patients with breast, colon, and renal cell carcinomas (4).

The prognosis of patients with brain metastases especially in the pretargeted therapy era is poor; the median survival time of untreated patients is ∼ 1 month (5). Brain metastases cause significant neurologic, cognitive, and emotional difficulties (6).

Conventional treatment has been whole brain radiation therapy (WBRT), which can rapidly abate many neurologic symptoms and thus improve quality of life. WBRT can also be associated with significant neurocognitive deficits. The key question, therefore, is "What is the balance between further neurologic decline from tumor progression or recurrence in the brain versus neurocognitive detriment due to damage from WBRT?"

The role of chemotherapy in the treatment of brain metastases is still being defined. Historically, poor chemosensitivity and the blood-brain barrier posed the largest obstacles. The advent of targeted agents with improved penetration into the central nervous system (CNS) has the potential to enhance response rates and improve the efficacy of WBRT.

We review new directions in brain metastases therapy, specifically focusing on improving the therapeutic ratio in these patients. Two principal themes are addressed: improving local control and reducing brain injury. Several developments have focused on enhancing the efficacy of WBRT, thereby increasing the time to neurologic failure. This has been shown with two radiosensitizers, efaproxiral (Efaproxyn, RSR-13; ref. 7) and motexafin gadolinium (Xcytrin), as well as promising new systemic agents that synergize (or are additive) with radiation by potentially crossing the blood-brain barrier, including temozolomide (Temodar; Schering Plough, Kenilworth, NJ; ref. 8), lapatinib (GlaxoSmithKline, London, United Kingdom; ref. 9), and MPC 6827 (Myriad, Salt Lake City, Utah). These agents are in the early clinical testing phase but could also potentially be used to treat micrometastatic disease in a so-called "prophylactic" setting in high-risk patients, thereby reducing the overt development and manifestation of brain metastases and delaying the use of cranial radiation therapy.

The introduction of highly advanced radiation delivery methods affords optimal conformal avoidance of eloquent areas of the brain, such as the hippocampus, which are at low risk of harboring microscopic disease but are critical in

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Table 1. Dose fractionation schemes in randomized trials of WBRT alone for brain metastases

Study	Year	No. patients	Randomization (Gy/no. fractions)	Median survival (mo)
Harwood and Simpson (87)	1977	101	30/10 vs 10/1	4.0-4.3
Kurtz et al. (88)	1981	255	30/10 vs 50/20	3.9-4.2
Borgelt et al. (89, 90)	1980	138	10/1 vs 30/10 vs 40/20	4.2-4.8
Borgelt et al. (89, 90)	1981	64	12/2 vs 20/5	2.8-3.0
Chatani et al. (91)	1986	70	30/10 vs 50/20	3.0-4.0
Haie-Meder et al. (92)	1993	216	18/3 vs 36/6 or 43/13	4.2-5.3
Chatani et al. (93)	1994	72	30/10 vs 50/20 or 20/5	2.4-4.3
Murray et al. (94)	1997	445	54.4/34 vs 30/10	4.5

maintaining neurocognitive function. Additionally, several pharmacologic agents with the potential for reducing neurologic injury are beginning to be tested with WBRT.

Conventional Treatment: Whole Brain Radiation Therapy

Conventional treatment for patients with widespread brain metastases uses WBRT, corticosteroids, and antiseizure medications, as needed, to attenuate symptoms. This approach can rapidly ameliorate many neurologic symptoms, improve quality of life, and is especially beneficial in patients who have brain metastases that impinge on eloquent areas or are too large, numerous, or disseminated for surgery or radiosurgery (10, 11). Table 1 summarizes results of different dose and fractionation schedules from eight randomized studies in patients with brain metastases who received WBRT alone, with median survival ranging from 2.4 to 4.8 months. The consensus from these studies of fractionation schedules is that differences in dose, timing, and fractionation have not significantly altered the median survival time for WBRT treatment of brain metastases, although there are differences in resulting neurocognitive side effects. Among the best predictors of survival is the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) class, a statistical method that creates a regression tree according to prognostic significance (Table 2) and groups patients according to age, Karnofsky performance status, and disease status (12). RPA class 1 patients with brain metastases who are younger, have higher Karnofsky performance status scores, and have controlled extracranial disease have the longest median survival following WBRT (Table 3). RPA class 2 and class 3 patients have half or less median survival compared with RPA class 1. The ultimate determination of the total dose and fractionation is usually made on the basis of RPA, patient and physician preference, expected outcomes, and potential for future therapies.

Complete or partial responses have been documented in more than 60% of patients in randomized controlled studies conducted by the RTOG (12). Some reports indicate that response to WBRT may be related to the primary histology. Nieder et al. (13) studied 108 patients and assessed CT response based on tumor type following WBRT alone. Overall, complete response was obtained in 24% of patients and partial response in 35%. Response rates ranged from 81% for small-cell lung carcinoma to 0% for malignant melanoma (although other series have shown response rates of 45-65% for melanoma brain metastases; Table 4; ref. 14). Retrospective investigations of treatment for brain metastases from various primaries suggest relatively clustered survival statistics: 6 months for female genitourinary cancers (15), 4.2 months for breast cancer (16), 2.3 months for melanoma (17), etc. The RTOG RPA multivariate analysis, however, did not find histology to be an independent predictor of survival following WBRT. The majority of patients who achieve local tumor control die from progression of extracranial disease, whereas the cause of death is most often due to CNS disease in patients with recurrent, progressive, or uncontrolled brain metastases (18).

It is important to recognize that there are some arguments against the use of WBRT. The ability to reverse neurologic symptoms has been debated and its use, especially in large doses per fraction, has been associated with debilitating complications in some long-term survivors (19, 20). Some question its utility given that, often, survival is unaltered whether upfront WBRT is used or not. In a disease process where the occurrence of brain metastases represents only one component of systemic spread, it is unlikely that local control of disease in one compartment will alter overall survival, and decisions about local disease control are not driven by the effect

Table 2. RPA classes for brain metastases

	Class 1	Class 2	Class 3
KPS score	≥70	≥70	<70
Primary disease status	Controlled systemic disease	Uncontrolled systemic disease	Uncontrolled systemic disease
Age (y)	≤65	>65	>65
Extracranial metastases	None	Present	Present

NOTE: Data from ref. 12.
Abbreviation: KPS, Karnofsky performance status.

Table 3. Median survival according to RPA class following WBRT

Treatment	Patients (*n*)	Median survival by RPA class (mo)		
		Class 1	Class 2	Class 3
WBRT (RTOG phase III trials; ref. 12)	1,176	7.1	4.2	2.3
RS (95)*	268	14.0	8.2	5.3
RS + WBRT (95)	301	15.2	7.0	5.5
Surgery + WBRT (96)	125	14.8	9.9	6.0

Abbreviation: RS, radiosurgery.
* Twenty-four percent of patients received salvage therapy with WBRT.

on survival but rather by the value of local control (21). Not surprisingly, trials (that were not designed to answer an overall survival question) of local therapies that have excluded WBRT show no difference in overall survival (22).

However, a cautionary observation is provided by a retrospective analysis from Germany; Pirzkall et al. (23) reported that for patients with brain metastases but without extracranial disease (i.e., patients with a much lower likelihood of dying from systemic metastases), the median survival following radiosurgery alone with WBRT used for salvage was 8.3 months, compared with 15.4 months for similar patients treated up-front with radiosurgery plus WBRT. Similar results were seen in a retrospective study from the Mayo Clinic with a survival benefit for adjuvant WBRT limited to patients without systemic disease, with 5-year survival rates of 21% for those who received adjuvant WBRT compared with 4% for those patients who did not (24). These observations are crucial, implying that for those patients whose prolonged survival is likely, such as breast cancer patients, failure to control the intracranial disease by omitting or delaying WBRT could potentially result in a negative survival effect.

The use of adjuvant WBRT following resection or radiosurgery has also been proved to be effective in terms of improving local control of brain metastases and thus decreasing the likelihood of neurologic death. Approximately 70% of patients with brain metastases experience relapse after resection, if WBRT is omitted (25).

Improving Outcomes: The Addition of Surgery or Radiosurgery

The addition of various modalities to WBRT to improve outcomes of patients with metastatic brain lesions has resulted in modest success for certain patient cohorts. Improved overall survival and local control has been shown in select cohorts of patients with single brain metastases with the addition of surgery or stereotactic radiosurgery to WBRT (26, 27).

The primary therapeutic objectives for resectable brain metastases are to remove known metastatic lesions and to prevent recurrence of intracranial disease. Even in apparently well-delineated tumors, surgery alone may not completely eliminate residual microscopic disease. A number of randomized studies, summarized in Table 5, have compared WBRT alone to WBRT plus surgery (25, 26, 28). In the absence of postoperative WBRT, there remains a high level of actuarial

relapse, ~70%, after surgery alone. Thus, the combination of surgical resection followed by WBRT has been established as a more effective treatment for control of metastatic brain disease compared with surgery or radiotherapy alone. Stated another way, WBRT following surgery for resectable oligometastatic disease significantly reduces local and regional failure and likely increases median survival time, compared with surgery alone. The strongest predictor of response following WBRT, whether alone or with radiosurgery or surgery, is by RPA class, as shown in Table 3. As stated above, RPA class 1 patients have median survival times essentially double those of patients in RPA class 2 or class 3 when treated with surgery plus postoperative WBRT.

Radiosurgery refers to the delivery of a single large dose of radiation to a small intracranial target, using a stereotactic localization system, and maximal head immobilization, frequently achieved by using a minimally invasive stereotactic head frame. This precise system allows optimal targeting of tumor regions while maximally and conformally avoiding healthy brain tissue. A number of studies in brain metastases from different disease sites have shown the efficacy of adding radiosurgery to conventional WBRT. In fact, radiosurgery improves survival in patients with single metastases and may also improve outcomes in patients with one to three metastases when used in conjunction with WBRT. Kondziolka et al. (29) compared WBRT alone to radiosurgery plus WBRT in 27 patients with multiple brain metastases and found the combined treatment approach to be superior in 1-year local failure rates, which were 100% and 8% in WBRT alone and radiosurgery plus WBRT groups, respectively. Median survival

Table 4. Response to WBRT in patients with brain metastases from various tumor types (*N* = 108)

Tumor type	Complete response (%)	Partial response (%)
Small cell carcinoma	37	44
Breast cancer	35	30
Squamous cell carcinoma	25	31
Adenocarcinoma (nonbreast)	14	36
Renal cell carcinoma	0	46
Melanoma	0	0
All metastases	24	35

NOTE: Data from Nieder et al. (13).

Table 5. WBRT with or without surgery and surgery with and without WBRT in randomized studies

Study	Year	n	Treatment	Local recurrence (% patients)	Median survival (mo)
Patchell et al. (26)	1990	48	WBRT	52	4
			WBRT + surgery	20	10
Noordijk et al. (28)	1994	63	WBRT	Not reported	6
			WBRT + surgery		10
Mintz et al. (97)	1996	84	WBRT	Not reported	6.3*
			WBRT + surgery		5.6
Patchell et al. (25)	1998	95	Surgery	46[†]	12.0
			Surgery + WBRT	10	10.8

*$P = 0.24$.
[†]$P = 0.001$.

times trended in favor of radiosurgery plus WBRT (7.5 versus 11.0 months; $P = 0.22$). These investigators concluded that combined WBRT plus radiosurgery boost significantly improved control of metastatic brain disease in patients with two to four brain metastases. Overall, in these and other studies (25, 26, 29), 1-year local control after WBRT alone has been approximately <15%, indicating a possible benefit from the combined use of radiosurgery and WBRT. A number of studies in brain metastases from different cancers, such as malignant melanoma (17), non–small-cell lung cancer (30), renal cell carcinoma, and gastrointestinal cancers (31), also support the use of WBRT combined with radiosurgery.

Perhaps the most compelling new data come from the first multisite, prospective, randomized study to evaluate the use of radiosurgery boost after WBRT in unresectable brain metastases. The RTOG 95-08 study enrolled 333 patients from 55 participating institutions, randomized to WBRT with or without radiosurgery boost. A significant survival advantage was observed in the WBRT plus radiosurgery boost group for patients with single unresectable brain metastases; median survival was 6.5 months in the boosted group, compared with 4.9 months for the control ($P = 0.0393$). Survival also was prolonged in patients with an RPA class 1 status who received the radiosurgery boost ($P = 0.0121$). Combination radiotherapy treatment also resulted in stable or improved Karnofsky performance status scores, improved local control, and a better complete response rate in all patients. The total number of patients with brain metastases from breast cancer in this trial was 34 (27).

Reducing Side Effects: Can Whole Brain Radiotherapy Be Omitted?

A key question related to the optimal use of WBRT is the identification of the appropriate patient populations in which WBRT should be part of routine treatment at the time that brain metastases are diagnosed. Some studies suggest (but without level 1 evidence) that WBRT may be omitted under certain circumstances. With the recent advent of radiosurgery, a new trend has been emerging in the management of patients with brain metastases; in this approach, patients with a limited number of brain metastatic lesions are treated with radiosurgery alone, without WBRT, and are then closely monitored, which

involves monthly or every other month magnetic resonance imaging. Repeat radiosurgery is done for new intracranial metastases, with the intent being avoidance or delay of WBRT in as many patients, and for as long as possible. The rationale for this is the avoidance of potential neurotoxicity from WBRT.

In the prospective randomized Japanese trial, JROSG 99-1, patients were randomized to radiosurgery alone versus whole brain radiotherapy and radiosurgery. The actuarial 6-month freedom from new brain metastases was 48% in the radiosurgery alone arm and 82% in the radiosurgery and whole brain radiotherapy arm (log-rank, $P = 0.003$). Actuarial 1-year brain tumor control rate for the lesions treated with radiosurgery was 70% in the radiosurgery alone arm and 86% in the radiosurgery and whole brain radiation arm (log-rank, $P = 0.019$; ref. 32). Another randomized trial compared radiosurgery alone versus whole brain radiotherapy and radiosurgery versus whole brain radiotherapy alone (33). The local brain control rate was highest in the radiosurgery plus WBRT arm. Clinical trial–based assessments therefore suggest enormously high rates of intracranial failures and reduced local control rates when WBRT is omitted or delayed.

The best evidence from the currently available trials suggests that optimal radiation treatment of brain metastases consists of a multimodal approach involving a combination of surgery or radiosurgery with WBRT in patients stratified by RPA class. In many cases, the addition of WBRT represents a conservative approach that can improve local control and delay intracranial recurrence.

Neurocognitive Impairment Conundrum: Tumor Progression or Radiation Injury?

Baseline neurocognitive function. Patients with brain metastasis may suffer a certain degree of neurocognitive function impairment from multiple factors, including the tumor, WBRT, neurosurgical procedures, chemotherapy, and other neurotoxic therapies (including anticonvulsants and steroids), or from paraneoplastic effects induced by the malignancy (34). Furthermore, radiotherapy variables (e.g., total dose, volume of brain irradiated, and fraction size) and the interaction with other treatment (e.g., concurrent chemotherapy) or patient variables (i.e., age and diabetes mellitus) all influence the

incidence of radiation-induced injury to the brain and may account for the differences in reported incidences of cognitive deficits (35, 36). In addition, conventionally used measures such as the Folstein mini-mental status examination are rather crude, and it is crucial to develop sensitive and practical neurocognitive function testing to characterize these changes (37). In particular, the sensitivity of mini-mental status examination has been shown to be problematic in detecting subtle neurocognitive dysfunction in patients with brain metastasis where clinically apparent WBRT-induced dementia is rare (1.9-5.1%; refs. 6, 19). All of these factors can potentially affect the manifestation of changes in neurocognition in a patient with newly developed brain metastases.

Recent evidence indicates that a battery of validated, language-specific, and population-normalized neurocognitive function tests evaluating memory, fine motor coordination, and executive functions confers more accurate and comprehensive measurement of neurocognitive function changes in patients with brain metastases (38). In a phase III clinical trial that compared WBRT (30 Gy in 10 fractions) versus WBRT plus motexafin gadolinium in patients with brain metastases, analysis of neurocognitive function data showed that 90.5% of patients had significant impairment (>1.5 SD from the age-adjusted population normalized score) in one or more neurocognitive domains at the time of diagnosis of brain metastasis, with 42% of the patients impaired in at least four of the eight tests (34, 39, 40).

Mechanism of radiation damage. The toxicity following radiation has been classically divided into three categories based on the timing of onset of symptoms: acute, subacute, and late (41). Acute effects occur during the first few weeks of treatment and are often characterized by drowsiness, headache, nausea, vomiting, and worsening focal deficits. Often, cerebral edema is the cause of these symptoms and corticosteroids may improve these symptoms. Subacute encephalopathy (early delayed reaction) occurring at 1 to 6 months after completion of radiation may be secondary to diffuse demyelination (42, 43). Symptoms include headache, somnolence, fatigability, and deterioration of preexisting deficits that resolve within several months. Late delayed effects appear more than 6 months after radiation and are generally irreversible and progressive (44). This may be a result of white matter damage due to vascular injury, demyelination, and necrosis. Symptoms range from mild lassitude to significant memory loss and severe dementia (45).

The pathophysiology of radiation-induced neurocognitive damage is complex and involves intercellular and intracellular interactions between vasculature and parenchymal cells, particularly oligodendrocytes, which are important for myelination. Oligodendrocyte death can occur due to direct p53-dependent radiation apoptosis or due to exposure to radiation-induced tumor necrosis factor α (46, 47). Postradiation injury to the vasculature involves damage to the endothelium leading to platelet aggregation and thrombus formation, followed by abnormal endothelial proliferation and intraluminal collagen deposition (35, 48). Further, hippocampal-dependent functions of learning, memory, and spatial information processing seem to be preferentially affected by radiation (49). Animal studies reveal that doses as low as 2 Gy can induce apoptosis in the proliferating cells in the hippocampus, leading to decreased repopulative capacity (50).

It has been speculated that the neurologic status and quality of life of patients in whom WBRT is withheld are superior. The only randomized data available in this context are from the Japanese trial mentioned earlier in which patients were randomized to radiosurgery alone or with WBRT; detailed neurocognitive assessments were not done, and the primary assessment was by an evaluation of performance status and neurologic functional status using RTOG criteria (32). There were no differences in these end points between the two study arms, belying the claims of worse neurologic outcomes in the WBRT arm. In fact, many have argued that the converse might be true: withholding WBRT increases intracranial failure and neurologic deterioration is more directly related to disease progression in the brain (51). In the recent phase III trial of WBRT with or without motexafin gadolinium, the most significant predictor for neurologic and neurocognitive decline, as well as deterioration in quality of life, was disease progression in the brain (34).

Prevention of Neurocognitive Impairment: Reducing Treatment-Related Injury

Although the neurocognitive conceptual framework for understanding the effects of radiotherapy is currently very limited, it seems that the pathophysiology of late radiotherapy injury is dynamic, complex, and a result of intercellular and intracellular interactions between the vasculature and parenchymal compartments, and injury is most likely multifactorial (i.e., demyelination, proliferative and degenerative glial reactions, endothelial cell loss, and capillary occlusion; ref. 49). The vascular hypothesis is probably the most recognized and longest standing premise as the primary cause of radiation-induced damage (52). Taken together, these mechanisms result in a picture similar to the small vessel disease, as is often seen with vascular dementia (53). For this reason, there is interest in using pharmaceutical agents that are effective in the treatment of vascular dementia for irradiated brain tumor patients.

Memantine. Memantine, a novel agent, is an N-methyl-D-aspartate receptor antagonist that blocks excessive N-methyl-D-aspartate stimulation that can be induced by ischemia and lead to excitotoxicity. It is believed that agents that block pathologic stimulation of N-methyl-D-aspartate receptors may protect against further damage in patients with vascular dementia (54). Thus, N-methyl-D-aspartate receptor antagonists such as memantine may be neuroprotective and prevent neuronal injury associated with radiation-induced ischemia. In addition, the physiologic function of the remaining neurons could be restored, resulting in symptomatic improvement (55). Preclinical *in vitro* and *in vivo* data support this hypothesis (56–58). Phase III clinical trials of memantine in patients with vascular dementia showed clinical benefit, with the subgroup of patients with small-vessel disease responding better to memantine than other types of dementia (59, 60). The RTOG plans a trial of memantine directed at preventing the detrimental effects of cranial radiation.

Hippocampal-sparing brain radiation therapy. Besides pharmaceutical interventions, others are considering modifying how WBRT is delivered to decrease the risk of neurotoxicity. Investigations are under way using new technology to conformally avoid the hippocampus (50). With the use of intensity-modulated radiotherapy, it is possible to create isodose distributions that treat the majority of the brain to full dose while keeping the radiation dose to the hippocampus relatively low. However, prospective trials with detailed neurocognitive function testing will be needed to determine if sparing of the hippocampus alone is beneficial or if other parts of the limbic system will also need to be spared, as well as to assess the potential effect on patterns of recurrence in the event that the whole brain is not irradiated.

Prevention of Neurocognitive Impairment: Enhancing Radiation Effect

Radiosensitizers and radioenhancers are intended to increase the effect of radiation therapy in tumors with less or no damage to normal tissue. The basic tenet is that by enhancing the radiation effect, time to neurologic progression or recurrence can be potentially increased. These agents have been studied in patients with brain metastases, in an effort to improve survival beyond 4 to 6 months, with mixed results. (refs. 19, 39, 61–66; Table 6). Recent developments suggest a new interest in this approach with two compounds that show promise as radiosensitizers: motexafin gadolinium and efaproxiral.

Motexafin gadolinium. Motexafin gadolinium is a metalloporphyrin redox modulator that shows selective tumor localization and catalyzes the oxidation of a number of intracellular reducing metabolites, such as ascorbate, glutathione, and $NADP^+$, thereby generating reactive oxygen species and depleting the pools of reducing agents necessary to repair cytotoxic damage (67). Selective uptake of motexafin gadolinium in tumors, but not in normal tissues, has been shown in patients by magnetic resonance imaging because of its paramagnetic characteristics (34, 39, 68, 69).

Preliminary studies in patients with brain metastases treated with motexafin gadolinium and WBRT showed radiologic responses in 68% to 72% of patients (40, 68). A large randomized phase III study of motexafin gadolinium in 401 patients did not show a significant increase in median survival (5.2 versus 4.9 months; $P = 0.48$) or median time to neurologic progression (9.5 versus 8.3 months; $P = 0.95$). However, when analyzed by tumor type, motexafin gadolinium significantly improved time to neurologic progression in the prespecified stratum of 251 patients with brain metastases from non–small-cell lung cancer (39). A confirmatory randomized phase III trial in patients with non–small-cell lung cancer has completed accrual and results are pending.

Efaproxiral. Efaproxiral (Efaproxyn, formerly RSR13, Allos Therapeutics, Westminster, CO) is a synthetic small molecule that noncovalently binds to hemoglobin and decreases its oxygen binding affinity and shifts the oxygen dissociation curve to the left, increasing p50 and tissue pO_2 (i.e., the pO_2 that results in 50% hemoglobin saturation). Thus, the radiosensitizing effect of efaproxiral is not dependent on its diffusion into tumor cells or on selective tumor uptake. It exerts its effects based on an increase in tumor oxygen levels, thereby circumventing restrictions due to the blood-brain barrier (70–73).

Shaw et al. (66) conducted a phase II study to evaluate efaproxiral plus WBRT in 57 patients with brain metastases. Median survival time for the efaproxiral-treated patients, who also received supplemental O_2, was 6.4 months compared with 4.1 months for the RTOG database ($P = 0.0174$). In an exact-matched case analysis ($n = 38$), median survival time for patients treated with RSR13 was 7.3 months versus 3.4 months for patients in the RTOG database ($P = 0.006$).

Subsequently, a phase III randomized, open-label, comparative study (REACH) of standard WBRT plus supplemental O_2 with or without efaproxiral was conducted in 538 RPA class 1 or class 2 patients with brain metastases (7). This study showed a nonsignificant increase in median survival for efaproxiral versus control (5.3 versus 4.5 months; $P = 0.17$), whereas median survival was nearly doubled in the subgroup of 115 patients with breast cancer (8.7 versus 4.6 months; $P = 0.061$, Cox multiple regression). The overall response rate in these patients was 72% for those treated with efaproxiral compared with 49% for control patients. A second study (ENRICH) of

Table 6. Randomized trials of cranial radiation therapy plus radiosensitizer in patients with brain metastases

Study	Year	No. patients	RE	Gy/no. fractions	Median survival time (mo), WBRT + RE vs WBRT
DeAngelis et al. (19)	1989	58	Lonidamine	30/10	3.9 vs 5.4
Eyre et al. (61)	1984	111	Metronidazole	30/10	3.0 vs 3.5
Komarnicky et al. (62)	1991	779	Misonidazole	30/6-10	3.9
Phillips et al. (63)	1995	72	BrdUrd	37.5/15	4.3 vs 6.1
Mehta et al. (39)	2003	401	MGd	30/20	5.2 vs 4.9
		251 NSCLC			Not reached vs 7.4*
Suh (64)	2004	5-38	Efaproxiral	30/10	5.4 vs 4.4
Stea et al. (65)	2004	107 BCA			4.5 vs 8.6*
Shaw et al. (66)	2003	57	Efaproxiral	30/10	6.4 vs 4.1*

Abbreviations: RE, radioenhancer; BrdUrd, bromodeoxyuridine; MGd, motexafin gadolinium; NSCLC, non–small cell lung cancer; BCA, breast cancer.
*$P < 0.05$.

efaproxiral in women with brain metastases from breast cancer began enrollment in 2004 with a target of 360 patients worldwide and has now closed to accrual. The only noteworthy side effect from efaproxiral is hypoxia, which is treated with supplemental oxygen for 1 to 2 h following efaproxiral administration until pO_2 levels return to normal. These recent results suggest that different radiosensitizers may be helpful in specific subsets of patients with brain metastases from lung and breast cancers.

Prevention of Neurocognitive Impairment: Prevention by Treating Micrometastatic Disease

One established method of treating micrometastatic disease in the preventative setting is with prophylactic cranial irradiation, such as in cases of small-cell lung cancer (74). This has been nested in the fact that in the vast majority of patients that undergo definitive treatment for the primary lung cancer, the brain is the predominant site of failure. Studies have shown an improvement in survival with the use of prophylactic cranial irradiation in small-cell lung cancer; however, the potential risk for radiation-related neurocognitive side effects remains, and thus other nonradiation approaches of treating and preventing micrometastatic disease continue to be explored (75).

The role of chemotherapy in the treatment of brain metastases is still being defined. One of the major limitations of cytotoxic chemotherapy is the presence of an intact or only partially disrupted blood-brain barrier, which limits the passage of drug into tumor; however, the development of newer drugs with improved penetration into the CNS has led to a number of clinical trials investigating these agents in addition to WBRT (76). These agents can be potentially used as radio-sensitizer similar to those mentioned in the preceding section, or, although in early clinical testing, the premise may be to use these agents alone to treat micrometastatic disease. This, in turn, would prevent the development of symptomatic brain metastases and would thus allow avoidance or at least delay in the need for cranial radiation therapy.

Temozolomide. Temozolomide is a recently developed second-generation oral alkylating prodrug that is converted to an active metabolite, 5-(3-methyltriazen-1yl)imidazole-4-carboximide, and has nearly 100% bioavailability. In addition, temozolomide readily crosses the blood-brain barrier, producing cerebrospinal fluid concentrations that are ∼30% of plasma concentrations (77). In limited preclinical studies, some synergy with radiation has been shown (29). Toxicity to temozolomide is general low, with <5% of patients experiencing myelosuppression (78).

Temozolomide has shown activity in patients with recurrent or newly diagnosed brain metastases from various malignancies (79). Recent trials of temozolomide with radiation therapy suggest a significant increase in response rates, especially for metastases from lung cancer. Antonadou et al. (76) studied 52 patients with brain metastases from solid tumors randomized to temozolomide plus WBRT compared with WBRT alone. In this study from the Hellenic Radiation Oncology Group, objective response was 96% (38% complete response and 58% partial response) for temozolomide plus WBRT compared with 67% (33% complete response and 33% partial response) for

WBRT alone (P = 0.017). Histology seems to have a bearing on the effect of temozolomide, as well as when it is used with radiotherapy. For example, in a phase II study of dose-intense alternating weekly regimen of temozolomide, the response rate was 24% for non–small-cell lung cancer, 19% for breast cancer, and 40% for melanoma (80). Thus, temozolomide and radiation therapy may have promise in patients with brain metastases, especially for those with lung cancer and melanoma.

MPC 6827. A novel microtubule poison and antivascular agent, MPC-6827, developed by Myriad Pharmaceuticals as a parenteral chemotherapeutic agent, has shown remarkable ability to penetrate the CNS. It achieves brain concentrations several hundredfold greater than plasma. It binds to the same or nearby site on β-tubulin as colchicine and paclitaxel and inhibits microtubule assembly. This inhibition of microtubule formation interferes with cell cycle G_2-M phase transition and leads to mitotic arrest.

In vitro, MPC-6827 displays proapoptotic activity, with potency at low nanomolar concentrations in multiple cancer types including breast cancer. Furthermore, in cell lines overexpressing the multidrug resistance pumps, the activity of MPC-6827 was similar to its activity in nonresistant cell lines, perhaps suggesting its utility in drug-resistant tumors. *In vivo*, in studies done with athymic mice, the activity was greater than or equal to that observed with paclitaxel, carboplatin, doxorubicin, and gemcitabine. MPC-6827 is currently in clinical testing, in phase I trials in patients with progressive brain disease.

Lapatinib. Lapatinib (GlaxoSmithKline), a novel targeted drug that can be administered orally and inhibits the tyrosine kinase of ErbB1 (epidermal growth factor receptor) and ErbB2 (HER2) receptors, has shown encouraging activity in several clinical studies (81–84). Although concurrent lapatinib with radiation has not previously been evaluated in humans, the experience of gefitinib, an ErbB1 (epidermal growth factor receptor) inhibitor, in patients with non–small-cell lung cancer suggested that small-molecule tyrosine kinase inhibitors as a class could prove efficacious in the treatment of brain metastases (85).

Approximately one third of women with HER2-positive metastatic breast cancer will eventually develop CNS metastases. Lapatinib is under investigation, both as a single agent and in combination with trastuzumab, in women with metastatic breast cancer. In preclinical models, dual blockade of epidermal growth factor receptor and HER2 with lapatinib seems to sensitize breast cancer cell lines to radiation (86). Currently, a phase II trial has been initiated to evaluate the safety and feasibility of lapatinib, given concurrently with and following whole brain radiotherapy (with or without radiosurgery) in patients with HER2-positive breast cancer metastatic to the brain.

Conclusion

In summary, WBRT continues to be a mainstay of treatment for brain metastases, and the recent trend has been the application of multimodal approaches that include WBRT, radiosurgery, surgery, systemic, and local chemotherapy, with some promising results. Patients with brain metastases are susceptible to deficits in neurocognition because of their natural disease progression and potentially also from the

treatments rendered. Innovative CNS-specific strategies for preventing and treating neurocognitive deficits are actively under investigation. Recent advances in targeted therapies as well as radiosensitizers with improved penetration into the brain are beginning to show a role in improving outcomes in selected patients. These agents have shown tumor specific uptake, normal tissue sparing, and tolerable and reversible toxicities. This should lead to a superior therapeutic ratio by enhancing the benefit derived from whole brain radiotherapy resulting in an improvement in neurocognitive decline, neurologic progression, and quality of life. In the future, these novel agents will likely be incorporated into the treatment paradigm to treat occult micrometastatic disease thereby further extending the time to neurologic progression and, consequentially, the need for radiation therapy and its associated side effects in patients who develop brain metastases.

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Targeted Therapy for Brain Metastases: Improving the Therapeutic Ratio

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