Current Landscape and Future Prospects of Radiation Sensitizers for Malignant Brain Tumors: A Systematic Review

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■ BACKGROUND: **Radiation therapy (RT) is the cornerstone of management of malignant brain tumors, but its efficacy is limited in hypoxic tumors. Although numerous radiosensitizer compounds have been developed to enhance the effect of RT, progress has been stagnant. Through this systematic review, we provide an overview of radiosensitizers developed for malignant brain tumors, summarize their safety and efficacy, and evaluate areas for possible improvement.**

■ METHODS: **Following PRISMA guidelines, PubMed, EMBASE, Cochrane, and Web of Science were searched using terminology pertaining to radiosensitizers for brain tumor RT. Articles reporting clinical evidence of non-antineoplastic radiosensitizers with RT for malignant central nervous system tumors were included. Data of interest were presumed mechanism of action, median overall survival (OS), progression-free survival (PFS), and adverse events.**

■ RESULTS: **Twenty-two unique radiosensitizers were identified. Only 2/22 agents (fluosol with oxygen, and efaproxiral) showed improvement in OS in patients with glioblastoma and brain metastasis, respectively. A larger study was not able to confirm the latter. Improved PFS was reported with use of metronidazole, sodium glycididazole, and chloroquine. There was a wide range of toxicities, which prompted change of schedule or complete discontinuation of 9 agents.**

■ CONCLUSIONS: **Progress in radiosensitizers for malignant CNS tumors has been limited. Only 2 radiosensitizers have shown limited improvement in survival. Alternative strategies such as synthetic drug design, based on a mechanism of action that is independent of crossing the blood-brain barrier, may be necessary. Use of drug development strategies using new technologies to overcome past challenges is necessary.**

INTRODUCTION

Brain tumors, primary or metastatic, are a significant cause of cancer morbidity and mortality in the United States.[1] With an estimated incidence of >25,000 in 2020 alone, primary malignant brain tumors result in approximately 16,000 deaths per year in the United States, with glioblastoma carrying the lowest 5-year survival, of 6.8%.[2] The aggressive growth and recurrence patterns of malignant brain tumors necessitate multimodal management, with radiation therapy (RT) being the cornerstone of treatment for most as per current National Comprehensive Cancer Network guidelines.[3]

Key words
- Brain tumor
- Chemotherapy
- Glioblastoma
- Metastasis
- Radiosensitizer
- Radiosurgery
- Radiotherapy

Abbreviations and Acronyms
AA: Anaplastic astrocytoma
CNS: Central nervous system
OS: Overall survival
PFS: Progression-free survival
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL: Quality of life
RCT: Randomized controlled trial
RT: Radiation therapy
RTOG: Radiation Therapy Oncology Group
VFD: Visual field deficit
VPA: Valproic acid

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RT relies on the generation of oxygen free radicals to induce irreversible DNA damage in the target tumor cells. Like most aggressive systemic tumors, malignant brain tumors have the capacity to alter their metabolism and survive in hypoxic conditions, a phenomenon termed the Warburg effect.[4-6] The downstream metabolites secondary to this metabolic switch, such as lactate, have been shown to contribute to radioresistance.[6] To overcome the challenge of radioresistance, the need to develop radiosensitizers has been recognized. An effective radiosensitizer would 1) enhance the effects of radiation in tumors, 2) not increase radiosensitivity of adjacent normal tissue, and 3) not cause significant side effects, to improve the therapeutic ratio of RT in patients with cancer.

Although many agents have been shown to improve the lethal effects of radiation in vitro, few have had proven success clinically and even fewer have shown efficacy in improving patient outcomes. In this systematic review of radiosensitizers in the management of malignant brain tumors, our objectives are to 1) provide an overview of the landscape of synthetic or natural nonantineoplastic radiosensitizers that have been used in the clinical setting for primary or metastatic central nervous system (CNS) tumors; 2) outline the presumed or established mechanism of action; 3) delineate potential chemical or biological shortcomings of these agents; and 4) propose potential strategies for improving safety and efficacy with a focus on the most promising agents.

METHODS

Search Terms

A systematic literature search was conducted on July 3, 2020 using guidelines from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[7] The databases PubMed, Cochrane, EMBASE, and Web of Science were searched with the help of a librarian for clinical studies and randomized controlled trials in English without publication date restriction up to date of search. The detailed search strategy can be found in **Supplementary Table 1**.

Eligibility Criteria

Titles and abstracts were screened by 2 independent reviewers (U.B. and B.M.S.) and were included for full text review if they contained information on clinical trials on patients with brain neoplasms treated with RT plus a radiosensitizer. Disagreements between authors were resolved by arbitration by A.M. Trials that studied agents that have established antineoplastic roles as per the PubChem online database were excluded.[8] Retrospective studies were excluded. A summary of the search using PRISMA guidelines can be found in **Figure 1**.

Data Extraction

Median overall survival (OS) and progression-free survival (PFS) data were extracted from each study. High-grade (grade 3 or 4) adverse events were also extracted. Data were extracted by 2 reviewers (B.S. and S.I.M.) independently and cross-verified to ensure accuracy. Any disagreement was discussed and resolved mutually.

RESULTS

Literature Search

The combination of search terms returned 9734 abstracts indexed in the Cochrane, Embase, PubMed, and Web of Science databases after removing duplicates. We excluded 9663 abstracts after screening titles and abstracts that did not fit inclusion criteria. In addition, we excluded 13 articles after screening full texts, discussion, and mutual agreement. The remaining 58 articles that met all inclusion criteria were included in the review and used for data extraction. Please refer to **Figure 1** for the PRISMA diagram.

Identified classes of radiosensitizers included synthetic nucleosides ($n = 2$), inorganic compound ($n = 1$), medical gases ($n = 4$), selective cyclooxygenase 2 inhibitor ($n = 1$), clofibrate redox modulator ($n = 1$), nitroimidazoles ($n = 4$), dinitroazetidine ($n = 1$), statin ($n = 2$), histone deacetylase inhibitor ($n = 1$), aminoquinoline alkaloid ($n = 1$), xanthine derivative ($n = 1$), biological bacterial extract ($n = 1$), deoxymonosaccharide ($n = 1$), and tetraline ($n = 1$). Details regarding classification and proposed mechanism of each therapy can be found in **Table 1**. **Table 2** shows the study characteristics and summarizes the outcomes. A complete list of adverse events reported for each agent is tabulated in **Table 3**.

Celecoxib

Mechanism of Action. Celecoxib is a selective cyclooxygenase 2 inhibitor. The proposed mechanism of radiosensitization by celecoxib is via the inhibition of prostaglandin E2, which is associated with radioresistance.[9] It has also been suggested to inhibit cellular repair of sublethal radiation damage and tumor angiogenesis and cause cell cycle redistribution.[10]

Clinical Evidence. A single-arm phase 1/2 trial of oral celecoxib has been reported, consisting of 27 patients with unresectable brain metastases.[10] OS of 8.7 months was reported. The medians for time to progression, time to neurologic progression, and functional independence time were 3, 6.25, and 6.7 months, respectively. Celecoxib was determined to be safe for use with RT for treatment of brain metastasis, but no follow-up phase 3 studies were found in our search that established its efficacy.

Adverse Events. No grade 3 or 4 adverse events were reported in patients receiving celecoxib.[10]

Efaproxiral

Mechanism of Action. Efaproxiral is a clofibrate that causes a decrease of hemoglobin-oxygen binding affinity by allosterically modifying hemoglobin, which facilitates oxygen release. It thereby enhances tumor oxygenation, increases production of damaging free radicals, and hence increases radiation sensitivity.[11-15]

Clinical Evidence. Five studies investigated the use of intravenous efaproxiral in the treatment of brain metastases, recurrent primary brain tumors, and glioblastoma.[11-13,15,16] Efaproxiral was well tolerated by patients with glioblastoma and brain metastases in 2 single-arm phase 1 trials.[15,16] Reported OS was 13.7 months.[16] Two phase 2 trials were reported with this premise in patients with glioblastoma and brain metastasis.[12,13] Patients with glioblastoma achieved an OS of 12.3 months, which was

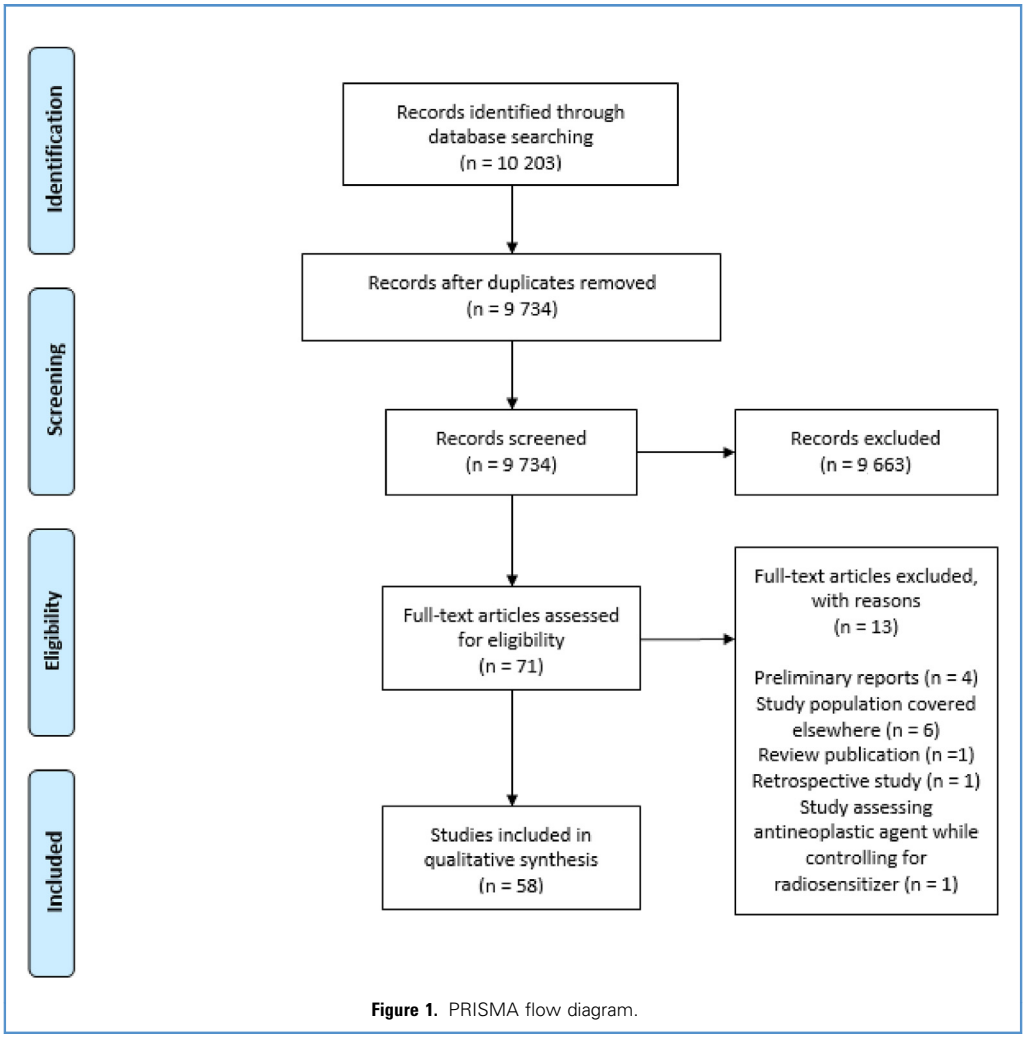

Figure 1. PRISMA flow diagram.

reported to be favorable compared with that observed in the NABTT (New Approaches to Brain Tumor Therapy) trials.[13] No pertinent phase 3 trials were identified. Patients with brain metastasis achieved an OS of 6.4 months in a phase 2 trial, which was significantly superior to the OS reported in similar patients in the RTOG (Radiation Therapy Oncology Group) database ($P = 0.006$).[12] A subsequent randomized controlled phase 3 trial investigated its efficacy in treatment of brain metastases.[11] OS was not significantly different between the trial and control group ($P = 0.16$). However, on subgroup analysis, the study noted particular survival improvement in patients with primary breast cancer metastases ($P = 0.003$), which was not seen in patients with metastasis from non-small-cell lung cancer ($P = 0.83$) or other cancers ($P = 0.85$). On further data analysis in a second study, significant benefit in OS, quality of life (QoL) during the first 6 months ($P = 0.019$) and quality-adjusted survival ($P = 0.001$) was noted in the efaproxiral treated arm.[11,14] The subsequent phase 3 ENRICH (Enhancing Whole Brain Radiation in Patients with Breast Cancer and Hypoxic Brain Metastases) study in patients with brain metastases from breast cancer failed to show improvement in OS and secondary end points including response rates, change in Karnofsky Performance Status, and neurologic symptoms.[17]

Adverse Events. A wide range of adverse effects were reported for efaproxiral. One study reported withholding doses of efaproxiral in 20% of patients because of toxicities,[15] and another reported discontinuing treatment in 10% of patients for the same reason.[12]

More prevalent high-grade adverse effects included headaches (2%–49%), nausea and vomiting (2%–45%), fatigue (5%–42%), hypoxemia (6%–41%), and dizziness (32%).[11-13,15,16]

Medical Gases

Mechanism of Action. Four combinations of medical gases were found to have been used as radiosensitizers: fluosol-dopamine with oxygen, carbogen, carbogen with nicotinamide, and hyperbaric oxygen. Fluosol is a perfluorocarbon and can carry large amounts of oxygen from a high P_{O_2} (partial pressure of oxygen)

Table 1. Clinically Evaluated Radiosensitizers and Their Suggested Mechanism of Actions

Radiosensitizer	Class	Proposed Mechanism of Action	Reference
2-Deoxy-D-glucose[71,72]	Deoxymonosaccharide	Inhibits glucose transport and glycolysis and DNA damage repair after radiation, enhancing injury in cellular systems with high rates of glycolysis	Mohanti et al., 1996[71]; Singh et al., 2005[72]
Bromodeoxyuridine (BrUrd)[50-58,63,64]	Synthetic nucleoside (halogenated pyrimidine)	Incorporates into DNA after being differentially taken up by tumor cells compared with normal brain cells	Kinsella et al., 1984[64]; Phuphanich et al., 1984[63]; Jackson et al., 1987[53]; Matsutani et al., 1988[55]; Hegarty et al., 1990[52]; Phillips et al., 1991[56]; Phillips et al., 1995[57]; Levin et al., 1995[54]; Groves et al., 1999[51]; Dabaja et al., 2003[50]; Prados et al., 2004[58]
Carbogen[19]	Medical gas	Promotes reoxygenation of chronically hypoxic cells to allow radiation-induced damage when given before and during radiation	Aquino-Parsons et al., 2008[19]
Carbogen and nicotinamide[21-23]	Medical gas (carbogen), vitamin B_3/niacin (nicotinamide)	See carbogen above	Fatigante et al., 1997[22]; Miralbell et al., 1999[21]; Simon et al., 2003[23]
Celecoxib[10]	Selective cyclooxygenase-2 inhibitor	Inhibits prostaglandin E_2 (PGE_2) production, which is associated with radioresistance. Also inhibits cellular repair of sublethal radiation damage and tumor angiogenesis and causes cell cycle redistribution	Cerchietti et al., 2005[10]
Chloroquine[66]	Aminoquinoline (alkaloid)	Induces apoptosis and the inhibits autophagy. May also increase the oxidative stress induced by radiotherapy	Rojas-Puentes et al., 2013[66]
Efaproxiral (RSR13)[11-13,15,16]	Clofibrate	Reduces Hb_{O_2} binding affinity by allosterically modifying hemoglobin and facilitating O_2 release, enhancing tumor oxygenation, and increasing radiation sensitivity	Kleinberg et al., 1999,[16] Kavanagh et al., 2001,[15] Kleinberg et al., 2002,[13] Shaw et al., 2003,[12] Suh et al., 2006[11]
Etanidazole[25-27]	2-nitroimidazole	Depletes glutathione and inhibits glutathione transferase, thereby enhancing the cytotoxicity of radiation	Chang et al., 1998,[26] Marcus et al., 2003,[27] Drzymala et al., 2008[25]
Fluosol/oxygen[18]	Perfluorocarbon (Fluosol), medical gas (oxygen)	Increases oxygen transport by carrying large amounts of O_2 from a high P_{O_2} environment and rapidly releasing O_2 when the environmental P_{O_2} is low	Evans et al., 1993[18]
Hyperbaric oxygen[24]	Medical gas	Increases oxygenation of all tissues including tumors, allowing generation of free radicals via radiation	Hartford et al., 2019[24]
Iododeoxyuridine (IdUrd)[53,59-62]	Synthetic nucleoside (halogenated pyrimidine)	Replaces thymidine during replication, increasing single-stranded and double-stranded DNA breaks. Dehalogenates with radiation, forming uracil free radical, leading to DNA strand breaks	Jackson et al., 1987[53]; Goffman et al., 1992[59]; Urtasun et al., 1993[62]; Sulvian et al., 1994; Schulz et al., 2004[60]
Lovastatin[49]	HMG CoA reductase inhibitor	Interferes with the ubiquitination of p27 thereby producing a G1 arrest	Larner et al., 1998[49]
Metronidazole[29,30]	Nitroimidazoles	Mechanism is unclear. Suggested to induce DNA damage via production of free radicals	Eyre et al., 1984[29]; Urtasun et al., 1976[30]
Mibefradil dihydrochloride[69]	Tetraline	Mechanism is unclear. Inhibits T-type calcium channels	Lester-Coll et al., 2018[69]
Misonidazole[32-44]	Nitroimidazoles	See metronidazole above	Jentzsch et al., 1977[36]; Bleehen et al., 1981[32]; Carabell et al., 1981[34]; Urtasun et al., 1982[43]; EORTC 1983[33]; MRC Working Party 1983[37]; Stadler et al., 1984[42]; Fulton et al., 1984[38]; Hatlevoll et al., 1985[35]; Shin et al., 1985[41]; Wara et al., 1986[44]; Nelson et al., 1986[40]; Komarnicky et al., 1991[39]

Continues

Table 1. Continued

Radiosensitizer	Class	Proposed Mechanism of Action	Reference
Pentoxifylline[68]	Xanthine derivative	Increases synthesis and release of prostacyclin and inhibits phosphodiesterase, increasing blood flow and tissue oxygenation	Johnson et al., 1998[68]
RRx-001[46]	Dinitroazetidine	Increases NO generation under hypoxic conditions, which increases blood perfusion and hence oxygenation. Also potentially induces generation of reactive oxygen species in cells, leading to DNA damage and tumor cell apoptosis	Kim et al., 2020[46]
Serratia marcescens[70]	Biological bacterial extract	Increases endogenous natural-kill-cell activity of peripheral-blood mononuclear cells against tumor cells and stimulates cytotoxicity by these cells	Black et al., 1993[70]
Simvastatin[48]	HMG CoA reductase inhibitor	Mechanism is unclear. Potentially inhibits mevalonate pathway, inhibiting posttranslational processing	El-Hamamsy et al., 2016[48]
Sodium glycididazole (CMNA)[28]	Nitroimidazole	Dysregulates ATM protein (ataxia telangiectasia mutated) protein pathway with irradiation to decrease radiation-induced DNA damage repair	Zeng et al., 2016[28]
Sodium nitrite[47]	Inorganic compound	Increases tumor blood flow and oxygenation by formation of NO from nitrite ion under low P_{O_2} and acidic pH. Also inhibits mitochondrial respiration thereby leaving more O_2 for reactive oxygen species production by radiation	Hosseini et al., 2015[47]
Valproic acid[65]	Histone deacetylase inhibitor, antiepileptic	Inhibits histone deacetylases by binding to the catalytic center of the enzyme. Induces cell accumulation in the G2/M phase of the cell cycle in vitro. Protects hippocampus-derived cells from radiation-induced cell killing	Krauze et al., 2015[65]

HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

environment and rapidly release this oxygen when the environmental P_{O_2} is low.[18] Similarly, carbogen, which is 95% O_2 and 5% CO_2, promotes reoxygenation of chronically hypoxic cells before and during irradiation and thereby increases the cytotoxic effects of radiation.[19] Hyperbaric oxygen increases oxygenation of all tissues including tumors, which allows generation of free radicals by radiation.[20]

Clinical Evidence. In a single-arm phase 1/2 trial in patients with anaplastic astrocytoma (AA) and glioblastoma, the combination of intravenous fluosol-dopamine and oxygen therapy in conjunction with RT showed minimal acute and no long-term toxicities. OS of 18.75 months was reported. Patients who survived >1 year showed a significantly prolonged survival compared with historical survival data ($P = 0.0013$).[18]

Inhalation of carbogen was investigated in children with brainstem gliomas and adults with glioblastoma.[19,21] No improvement in prognosis was noted with the addition of carbogen over historical prognosis (OS, 9.6–10.1 years).[19,21]

Three phase 1/2 studies evaluated the tolerability of carbogen and nicotinamide combination as a radiosensitizer for patients with glioblastoma. Although an initial study reported acceptable toxicity,[22] subsequent studies showed low tolerability.[21,23] OS ranged from of 9.2 to 11.1 months.[21-23] Time to progression reported in 1 study for the combination therapy was 5.8 months.[21] No significant improvement in survival was found in the 3 studies study compared with historic survival controls.[21-23]

One study evaluated survival and QoL with the use of hyperbaric oxygen before stereotactic radiosurgery in patients with brain metastasis.[24] OS in patients receiving hyperbaric oxygen was 1.4 years, which was statistically comparable to 1.0 year survival in matched control patients (P value not reported). No decrement in QoL was noted.

Adverse Events. Pneumonia and congestive heart failure were reported in 6% patients treated with fluosol/oxygen.[18]

More prevalent side effects related to nicotinamide included vomiting (8%–30%), neurotoxicity (9%–21%), intracranial hypertension (25%–32%), and seizures (13%).[21-23] Carbogen and nicotinamide treatment was discontinued in 6% of patients in 1 study because of toxicities.[22] One study[21] was able to administer uninterrupted treatment with combinations of carbogen and/or nicotinamide to only 72% of patients. Gastrointestinal intolerance accounted for 40% of interruptions in nicotinamide dosing, whereas dizziness, skin rash, and neurologic toxicities accounted for 10% of interruptions.[21]

Patients receiving hyperbaric oxygen did not experience any grade 3 or 4 adverse effects.[24]

Table 2. Summary of Studies on Radiosensitizers for Malignant Brain Tumors

Radiosensitizer	Reference	Pathology	Design/ Phase	Number of Patients	Age Range (years)	Outcomes	Control Group Outcomes
2-Deoxy-D-glucose	Mohanti et al., 1996[71]	Glioma grade 3 and 4	Phase 1/2	20	21–64	OS: 13 months	N/A
	Singh et al., 2005[72]	GBM	Phase 2	12	30–67	NR	N/A
Bromodeoxyuridine	Phuphanich et al., 1984[63]	GBM	Phase 1	12	25–77	NR	N/A
	Kinsella et al., 1984[64]	GBM (14), brain metastasis (7)	Phase 1	21	20–60	OS: 12 months	N/A
	Phillips et al., 1995[57]	(Treatment arm/control arm)breast (n = 1/1), lung (n = 24/25), other (n = 9/10)	RCT	70	30–78	OS: 4.3 months	OS: 6.12 months
	Prados et al., 2004[58]	AA (other than GBM)	Phase 3	190	≥18	OS: 55.2 months	OS: 49.2 months
	Phillips et al., 1991[56]	GBM	Phase 2	160	19–80	OS: 12.8 months	N/A
	Hegarty et al., 1990[52]	AA grade 3 (n = 5), GBM grade 4 (n = 18)	Phase 1	23	20–71	OS: 20 months	N/A
Bromodeoxyuridine	Matsutani et al., 1988[55]	GBM (n = 9), AAs (n = 2), well-differentiated astrocytomas (n = 4), malignant meningioma (n = 1), choroid plexus carcinoma (n = 1), malignant lymphoma (n = 1), metastatic cancers from lung tumors (n = 5)	Phase 1	23	13–74	NR	N/A
	Jackson et al., 1987[53]	Anaplastic astrosarcoma (n = 8), GBM (n = 50), unconfirmed diagnosis (n = 2)	Phase 1	60	No exclusion by age	OS: 13 months	N/A
	Dabaja et al., 2003[50]	Primary central nervous system lymphoma (n = 12)	Phase 1	12	34–66	OS: 18 months	N/A
	Levin et al., 1995[54]	AA (n = 116), astrocytoma stratum (n = 22)	Phase 2	138	18–74	NR	N/A
	Groves et al., 1999[51]	GBM (n = 88)	Phase 2	70	19–70	OS: 11.5 months	N/A
Carbogen	Aquino-Parsons et al., 2008[19]	High-grade brainstem glioma or diffuse brainstem tumor	Prospective trial	10	<18	OS: 9.6 months	N/A
Carbogen and nicotinamide	Fatigante et al., 1997[22]	GBM	Phase 1/2	36	20–71	OS: 10 months	N/A
	Miralbell et al., 1999[21]	GBM	Phase 1/2	107	29–71	OS for carbogen: 10.1 months OS for nicotinamide: 9.7 months OS for combined therapy: 11.1 months TTP for carbogen: 6.7 months TTP for nicotinamide: 4.8 months TTP for combined therapy: 5.8 months	N/A
	Simon et al., 2003[23]	GBM	Phase 2	71	35–70	OS: 8.4 months	OS: 8.1 months

Continues

Table 2. Continued

Radiosensitizer	Reference	Pathology	Design/ Phase	Number of Patients	Age Range (years)	Outcomes	Control Group Outcomes
Celecoxib	Cerchietti et al., 2005[10]	Primary tumor site: lung (n = 11), breast (n = 7), melanoma (n = 3) and other (n = 6, not lymphoma or germinal cell tumors)	Phase 1/2	27	43–76	OS: 8.7 months PFS: 3 months	N/A
Chloroquine	Rojas-Puentes et al., 2013[66]	Metastasis from primary tumor site: NSCLC and others (n = 58) and breast (n = 15)	Phase 2	73	18–80	OS: 10.2 months	OS: 7.42 months
Efaproxiral (RSR13)	Suh et al., 2006[11]	Metastasis from primary site: NSCLC (n = 291), breast (n = 108) and other (n = 116), not including small-cell lung cancer, germ cell tumors, and lymphomas)	Phase 3	515	≥18	OS: 5.4 months	OS: 4.4 months
	Shaw et al., 2003[12]	(Treatment arm/control arm) breast =18/113, lung = 33/698, melanoma (3/38), genitourinary (3/54) and unknown (0/167)	Phase 2	57	≥18	OS: 6.4 months	OS:4.1 months
	Kavanagh et al., 2001[15]	Metastasis from ovary, uterine cervix, prostate, breast, or soft tissue sarcoma	Phase 1/2	20	36–74	NR	N/A
	Kleinberg et al., 1999[16]	GBM	Phase 1	19	37–76	OS: 13.7 months	N/A
	Kleinberg et al., 2002[13]	GBM	Phase 2	50	≥18	OS: 12.3 months	N/A
Etanidazole	Drzymala et al., 2008[25]	Primary brain tumors and brain metastases. (individual diagnoses not reported)	Phase 1	47	NR	NR	N/A
Etanidazole	Chang et al., 1998[26]	AA (19) and GBM (50)	Phase 1	70	20–79	OS of GBM: 1.1 years OS of AA: 3.1 years	N/A
	Marcus et al., 2003[27]	Diffuse brainstem glioma (18)	Phase 1	18	4–26	OS: 8.5 months	N/A
Fluosol/oxygen	Evans et al., 1993[18]	GBM (15), AA (3)	Phase 1/2	18	16–72	OS: 17.3 months	OS: 12.4 months
Hyperbaric oxygen	Hartford et al., 2019[24]	Brain metastasis (38)	Prospective trial	38	NR	OS: 16.8 months	OS: 12 months
Iododeoxyuridine (IdUrd)	Sullivan et al., 1994[61]	AA (21) or GBM (18)	Phase 2	39	19–71	OS for entire cohort: 23 months OS for GBM: 15 months	N/A
	Goffman et al., 1992[59]	GBM or AA	Phase 1/2	45	>18	OS: 11 months	N/A
	Schulz et al., 2004[60]	GBM (26), AA (5)	Phase 1	31	21–73	Mean TTP: 5.5 months Mean OS: 10.9 months	N/A
	Urtasun et al., 1993[62]	AA (21), GBM (56), other unspecified (2)	Phase 1	79	18–75	OS (long infusion): 13.4 months OS (short infusion): 10.9 months	N/A
	Jackson et al., 1987[53]	AA (8) and GBM (50), histologic diagnosis was not obtained in 2 patients	Phase 1	60	NR*	OS: 13 months	N/A

OS, overall survival; N/A, not available; GBM, glioblastoma; NR, not reported; AA, anaplastic astrocytoma; TTP, time to progression; PFS, progression-free survival (median, unless otherwise stated); NSCLC, non-small-cell lung cancer; RCT, randomized controlled trial; CF, conventionally fractionated; MDF, multiple daily fractionated; RT, radiation therapy.

*All reported survival was converted from days, weeks, and years to months for simplicity by using the following equivalents: 30.417 days = 1 months; 4.345 weeks = 1 month; 1 year = 12 months.

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Table 2. Continued

Radiosensitizer	Reference	Pathology	Design/ Phase	Number of Patients	Age Range (years)	Outcomes	Control Group Outcomes
Lovastatin	Larner et al., 1998[49]	AA and GBM. *Outcomes not reported separately for each type of tumor	Phase 1/2	18	19—68	NR	N/A
Metronidazole	Eyre et al., 1984[29]	(Treatment/control): metastasis from breast (8/5), lung (33/36), other (16/13)	RCT	111	Not clearly defined	OS: 2.8 months	OS: 3.2 months
	Urtasun et al., 1976[30]	GBM	RCT	36	NR*	OS: 6 months	OS: 3.5 months
Mibefradil dihydrochloride	Lester-Coll et al., 2018[69]	GBM	Phase 1	19	NR	OS: 9 months PFS: 3 months	N/A
Misonidazole	Carabell et al., 1981[34]	AA (18), GBM (14)	Phase 2	49	18—70	OS (AA): 12.75 months OS (GBM): 7.5 months	N/A
	Hatlevoll et al., 1985[35]	AA, GBM	RCT	244	20—69	OS: 8—12 months	OS: 8—12 months
	Jentzsch et al., 1977[36]	Primary brain tumors (9), brain metastasis (3)	Phase 1	12	15—74	NR	NR
	EORTC 1983[33]	AA, GBM, and other gliomas	RCT	163	16 and older	Mean survival: 11.1 months, mean PFS: 7.5 months	Mean survival: 11.5 months, mean PFS: 7.5 months
	Komarnicky et al., 1991[39]	(Treatment/control): metastasis from breast (46/45), lung (236/254), other (82/76), unknown (22/18)	Phase 3	779	17—75	OS: 3.8—4.0 months	OS: 4.9—5.7 months
	Wara et al., 1986[44]	Medulloblastoma, ependymoma, astrocytoma (3/4), oligodendroglioma	Phase 1/2	29	4—27	OS: 13 months	N/A
	Urtasun et al., 1982[43]	AA (15) and GBM (44)	RCT	59	Mean: 56	OS: 6.2 months	OS: 6 months
	Bleehen et al., 1981[32]	Astrocytoma grade 3/4	RCT	55	18—75	OS: 8.9 months	OS: 7.2 months
	MRC Working Party 1983[37]	AA (161), GBM (203), undetermined grade 3/4 (20)	RCT	384	18—70	OS: 8.25 months	OS: 9 months
	Shin et al., 1985[41]	(Treatment/control): malignant astrocytoma (13/23), GBM (30/58)	RCT	124	Not clearly defined	OS: 11.3 months PFS: 8.1 months	OS: 6.2 months PFS in CF and MDF: 6.2 and 9 months, respectively
	Stadler et al., 1984[42]	Astrocytoma grade 3/4	RCT	45	Not clearly defined	OS: 13.8 months	OS: 9.8 months
	Nelson et al., 1986[40]	(Treatment/control): AA (47/10) and GBM (8/52). *Remainder of patients did not have a histologic diagnosis	RCT	293	18—70	OS: 10.7 months PFS: 7.2 months	OS: 12.6 months PFS: 7.4 months
	Fulton et al., 1984[38]	(Treatment/control): AA (13/26), GBM (24/65)	RCT	128	18—70	OS: 11.5 months TTP: 7.4 months	OS (CF) RT: 6.7 months OS (MDF RT): 10.3 months TTP (CF): 5.1 months TTP (MDF): 6.2 months
Pentoxifylline	Johnson et al., 1998[68]	Metastasis from lung (12) and other organs (2)	Phase 2	14	Not clearly defined	OS: 1.1 months	N/A

Continues

Table 2. Continued

Radiosensitizer	Reference	Pathology	Design/ Phase	Number of Patients	Age Range (years)	Outcomes	Control Group Outcomes
RRx-001	Kim et al., 2020[46]	Brain metastasis	Phase 1/2	22	Mean 59.2, standard deviation 12.9	OS: 5.2 months	N/A
Serratia marcescens	Black et al., 1993[70]	AA (4) and GBM (11)	Phase 1	15	31–69	OS: 18.0 months TTP: 7.7 months	N/A
Simvastatin	El-Hamamsy et al., 2016[48]	(Treatment/control): metastasis from breast (7/8), lung (13/16), other organs (5/1)	Randomized open-label pilot study	50	>18	OS: 3.4 months PFS: 1.6 months	OS: 3 months PFS: 1.5 months
Sodium glycididazole (CMNA)	Zeng et al., 2016[28]	(Treatment/control): metastasis from NSCLC (32/32)	RCT	64	29–85	OS: 11 months PFS: 7 months	OS: 9 months PFS: 4 months
Sodium nitrite	Hosseini et al., 2015[47]	(Treatment/control): metastasis from breast (4/4), other organs (6/6)	RCT (pilot)	20	18–80	NR	NR
Valproic acid	Krauze et al., 2015[65]	GBM	Phase 2	37	>18	OS: 29.6 months PFS 10.5 months	N/A

OS, overall survival; N/A, not available; GBM, glioblastoma; NR, not reported; AA, anaplastic astrocytoma; TTP, time to progression; PFS, progression-free survival (median, unless otherwise stated); NSCLC, non-small-cell lung cancer; RCT, randomized controlled trial; CF, conventionally fractionated; MDF, multiple daily fractionated; RT, radiation therapy.

*All reported survival was converted from days, weeks, and years to months for simplicity by using the following equivalents: 30.417 days = 1 months; 4.345 weeks = 1 month; 1 year = 12 months.

Nitroimidazoles

Mechanism of Action. Nitroimidazoles are a group of heterocyclic compounds commonly used as antibiotics with a broad spectrum of activity. Four nitroimidazoles have been studied in clinical trials. These nitroimidazoles include etanidazole, sodium glycididazole (CMNA), metronidazole, and misonidazole. Etanidazole depletes glutathione and inhibits glutathione transfer, which reduces the capability of the cell to break down reactive oxygen species, and hence increases the susceptibility of tumor cells to radiation.[25-27] Sodium glycididazole regulates the ATM (ataxia telangiectasia mutated protein) pathway, which is normally involved in radiation-induced DNA damage repair.[28] Metronidazole and misonidazole both mimic oxygen and enhance DNA damage induced by radiation.[29-31]

Clinical Evidence. Intravenous infusion of etanidazole was studied in 3 single-arm phase 1 trials, which included patients diagnosed with glioblastoma,[26] AA,[26] diffuse brain stem glioma,[27] and recurrent or refractory primary and metastatic brain tumors.[25] Two trials established safe doses of etanidazole at which the agent would be theoretically effective with manageable toxicity.[26,27] OS of 1.1 years reported in 1 study for patients with glioblastoma and 3.1 years for patients with AA was similar to historical survival data.[26] In pediatric diffuse brain stem gliomas, OS of 8.5 months was recorded, which was nonsuperior to that of historic control.[27]

Intravenous sodium glycididazole was studied in patients with brain metastases from non-small-cell lung cancer in a randomized controlled trial (RCT) and found to have an OS of 11 months, which was comparable to the OS of 9 months in the control group ($P = 0.418$). However, PFS of the study group (7 months) was longer than that of the control group (4 months) ($P = 0.038$). There was no difference in treatment-related toxicity between the groups ($P > 0.05$).[28]

Two RCTs incorporated oral metronidazole in the treatment regimen for radiosensitization.[29,30] Metronidazole achieved an OS of 12 weeks in patients with brain metastases.[29] This OS was not significantly different from the OS of 14 weeks reported in the control group ($P = 0.802$). In patients with glioblastoma, an OS of 26 weeks in the treatment group was achieved compared with 15 weeks in the control group.[30] Statistical significance of this result was not reported. The study also suggested an increase in PFS by 4.5 months in the metronidazole group ($P = 0.02$).[30]

Thirteen studies were identified that studied the use of oral misonidazole as a radiosensitizer.[32-44] In the first phase 1 trial conducted with misonidazole, the agent was determined to be safe, with reversible toxicity in patients with primary brain tumors and brain metastases.[36] Two additional phase 1/2 trials reported tolerable toxicity in patients with glioblastoma, AA, ependymoma, medulloblastoma, and oligodendroglioma, but OS was only comparable to survival in historical controls (OS, 7.5–13 months).[34,44] In a subsequent phase 3 trial in patients with brain metastases,[39] addition of misonidazole to RT did not confer a favorable prognosis compared with prognosis in patients receiving RT alone (OS, 3.8–4.0 months vs. 4.9–5.7 months, respectively). Additional RCTs in patients with various tumor types were also conducted, with control arms being RT alone. In the largest RCT

Table 3. Adverse Reactions for Radiosensitizers in Clinical Trials

Radiosensitizer	Myelo suppression (%)	Skin Toxicity (%)	Nausea/ Vomiting (%)	Hepato toxicity (%)	Hematologic Toxicity (%)	Neurologic Toxicity (%)	Mucositis/ Stomatitis (%)	Gastro intestinal Toxicity (%)	Infusion-Related Reaction (%)	Other (%)
2-Deoxy-D-glucose[71,72]	NR	NR	45	NR	NR	70	NR	NR	NR	Sweating 45 Drowsiness 30 Giddiness 10 Seizure 5—10 Disorientation 5 Somnolence 83 Intellectual deficit 83 Functional competence deficit 83 Memory deficit 83 Cognitive function deficit 20
Bromodeoxyuridine[50-58,63,64]	3— ≥74	1—57	6—67	1—17	NR	1—19	5—61	3—6	1	Pneumonia 1 Anorexia 33 Nail changes 15—17 Ototoxicity 1 Other unspecified toxicities 9
Carbogen[19]	NR	NR	NR	NR	NR	17	NR	NR	NR	
Carbogen and nicotinamide[21-23]	NR	2—9	8—30	7	NR	9—21	NR	NR	3	Ototoxicity 2—4 Epilepsy 13 Cranial hypertension 25—32
Celecoxib[10]	No grade 3 or 4 adverse events									
Chloroquine[66]	No adverse events in the treatment arm in addition to those in the control arm									
Efaproxiral (RSR13)[11-13,15,16]	NR	4	2—≥45	NR	NR	NR	NR	3	5	Hypoxemia 6—41 Headache 2—49 Fatigue 5—42 Dizziness 32 Alopecia 28 Creatinine increases 4 Sepsis 4 Respiratory failure 2 Cerebral edema 5 Dyspnea 5 Seizures 5 Hypotension 2
Etanidazole[25-27]	NR	6	2—6	NR	NR	11	NR	NR	11	Myalgia 2 Necrosis 4 Visual field deficit 2 Cramping-arthralgia syndrome (unspecified percentage)

Fluosol/oxygen[18]	NR	NR	NR	NR	NR	NR	NR	NR	NR	Pneumonia 6 Congestive heart failure 6
Hyperbaric oxygen[24]	No grade 3 or 4 adverse events									
Iododeoxyuridine (IdUrd)[53,59-62]	NR	3—8	NR	1—10	5—27	1—3	NR	1—3	NR	Deep vein thrombosis 3—4 Subclavian venous thrombosis 5 PE 7 Brain abscess 2 Pneumonia 2 Facial cellulitis 3
Lovastatin[49]	NR	NR	NR	NR	NR	NR	NR	NR	NR	Arthralgia 11
Metronidazole[29,30]	NR	NR	6—51	NR	NR	NR	NR	NR	NR	
Mibefradil dihydrochloride[69]	Adverse events not reported									
Misonidazole[32-44]	NR	1—10	2—22	0.5	0.3—0.5	0.5—22	1	6—9	0.8—13	Ototoxicity 4—9 Organic psychosyndrome 11 PE 0.5 Fever 1—6 Worsening of pervious heart condition 0.5
Pentoxifylline[68,*]	NR	NR	28	NR	NR	NR	NR	NR	NR	Dizziness 28 Headache 14 Tremor 7 Palpitations 7
RRx-001[46]	NR	NR	NR	3	≥3	≥3	NR	≥3	31	Asthenia 7 Metabolic disorder ≥3 Psychiatric disorders ≥3 Dyspnea 3 Pericardial effusion 3 Infections ≥3
Serratia marcescens[70]	NR	NR	≥7	NR	NR	NR	NR	13	≥53	Headache 27 Chills 53 Fatigue 13 Arthralgia/myalgia 7 Back pain 20 Hypotension 13
Simvastatin[48]	No adverse events in treatment arm in addition to those in control arm									
Sodium glycididazole (CMNA)[28]	No major adverse effects									
Sodium nitrite[47]	No major adverse effects									
Valproic acid[65]	NR	NR	NR	NR	NR	NR	NR	NR	NR	Metabolic derangement 7 Mental status change 10

NR, not reported; PE, pulmonary embolism.
*Toxicities were not graded by the study.

with misonidazole in patients with AA and glioblastoma,[37] no evidence of improvement in survival of study arm was found compared with survival in placebo control (OS, 8.25 vs. 9 months, respectively; P = 0.7). Another similar RCT[33] also showed no difference in mean survival or PFS between the study and control arms (mean survival, 11.1 vs. 11.5 months, P value nonsignificant, mean PFS, 7.5 vs. 7.5 months, P value nonsignificant, respectively). A study enrolling patients with AA and brain metastases[32] reported an OS of 9.7 months, similar to that in the control group (P value not reported). The remaining 6 studies[35,38,40-43] evaluated treatment of patients with AA or glioblastoma with misonidazole and RT. All 6 of these studies failed to show improvement in outcomes with the addition to misonidazole compared with RT alone (OS, 3.25–13.8 months; PFS, 7.2–8.75 months in study arm).

Adverse Events. The common reported side effect of etanidazole was neurologic toxicity (11%–28%).[25-27]

Patients receiving sodium glycididazole reported adverse effects that were not significantly different from those experienced by the control group.[28]

The only reported side effects for metronidazole were nausea and vomiting, with 6%–51% patients experiencing these.[29,30] Of patients, 6%–91% stopped the treatment regimen because of nausea and vomiting.[29,30]

One of the most common reported adverse effect of misonidazole, as reported in 9 studies,[33,34,36-38,40-42,44] was central and peripheral neuropathy (0.5%–20%). One study[45] reported dose modification in 9% of patients secondary to gastrointestinal toxicities.

RRx-001

Mechanism of Action. RRx-001 is a synthetic dinitroazetidine that is understood to increase nitric oxide generation under hypoxic conditions and increase blood perfusion to these tissues. Evidence also suggests that it induces generation of reactive oxygen species in cells, leading to DNA damage and cell apoptosis.[46]

Clinical Evidence. RRx-001 with RT was well tolerated in patients with brain metastasis in a single-arm phase 1/2 study. OS of this patient group was 5.2 months.[46] Studies establishing efficacy were not found.

Adverse Events. The most common adverse event attributable to RRx-001 therapy was infusion-related reaction (31%).

Sodium Nitrite

Mechanism of Action. Sodium nitrite is an inorganic compound that is suggested to inhibit mitochondrial respiration, thus sparing oxygen for radiation-induced damage, and also to increase tumor blood flow and oxygenation.[47]

Clinical Evidence. In a pilot randomized controlled study measuring radiologic response in patients with brain metastases,[47] intravenous sodium nitrite showed no improvement in tumor response from baseline in the treatment group compared with that of the control group.

Adverse Events. No major adverse effects were reported.[47]

Statins

Mechanism of Action. Simvastatin and lovastatin belong to the statin group, and their role as a radiosensitizer is still under investigation. Simvastatin is postulated to inhibit the mevalonate pathway, which thereby inhibits posttranslational processing.[48] Lovastatin interferes with the degradation of p27 and hence arrests the cells in G1 phase and prevents cell proliferation.[49]

Clinical Evidence. One study using oral simvastatin in patients with brain metastases[48] showed a median PFS of 1.6 months and OS of 3.4 months in the treatment group compared with a median PFS of 1.47 months and OS of 3 months in the nonplacebo control group. The improvement was not statistically significant (P = 0.880).[48]

A single-arm phase 1 trial of high-dose lovastatin for patients with glioblastoma and AA[49] concluded that lovastatin was tolerable in the given patient population. Survival outcomes were not reported.[49]

Adverse Events. No adverse events were reported in the treatment arm in addition to those in control arm.[48]

The only reported side effect for lovastatin was joint pain (11%).[49]

Synthetic Nucleosides

Mechanism of Action. Two synthetic nucleotides, bromodeoxyuridine and iododeoxyuridine, were identified. The proposed mechanism of action for bromodeoxyuridine as a radiosensitizer is unclear, although studies[50-58] have suggested that this compound is differentially taken up in tumor cells compared with normal brain cells and incorporated into DNA. Similarly, iododeoxyuridine acts as a replacement of thymidine during DNA repair and increases the incidence of single-stranded and double-stranded DNA break.[53,59-62]

Clinical Evidence. Eleven trials were conducted using bromodeoxyuridine as a radiosensitizer administered either intravenously[50,51,53-58,63,64] or intra-arterially.[52] Eight single-arm phase 1 and 2 trials were conducted for evaluation of safety and efficacy of bromodeoxyuridine in patients with glioblastoma, AA, astrocytoma stratum, malignant meningioma, choroid plexus carcinoma, primary CNS lymphoma, and brain metastasis.[50-52,54-56,63,64] One study concluded that intravenous bromodeoxyuridine resulted in significant neurologic toxicity in patients with primary CNS lymphoma and deemed it to be unsafe.[50] However, intra-arterial administration of the agent was determined to be safe in patients with glioblastoma,[52] and intermittent intravenous infusion resulted only in reversible myelosuppression and stomatitis.[55] Conversely, 2 phase 1 trials in patients with glioblastoma[63,64] reported tolerable toxicity based on the dosing schedule. OS data were deemed favorable compared with historical controls in this group (OS, 13 months).[53] Conclusions of phase 2 trials were also variable. Whereas 1 trial[51] concluded that bromodeoxyuridine did not extend survival in patients with glioblastoma compared with survival in historical control, 2 phase 2 trials[54,56] suggested that survival in the study groups was superior to historical survival data. These results formed the basis of subsequent phase 3 trials. OS ranged from 12 to 20 months across the phase 1 and 2 trials.[50-52,54-56,63,64]

In the largest phase 3 trial in patients with AA receiving radiation and chemotherapy,[58] addition of bromodeoxyuridine did not confer a significant survival advantage over patients receiving radiation and chemotherapy alone. OS was 4.6 years and 4.1

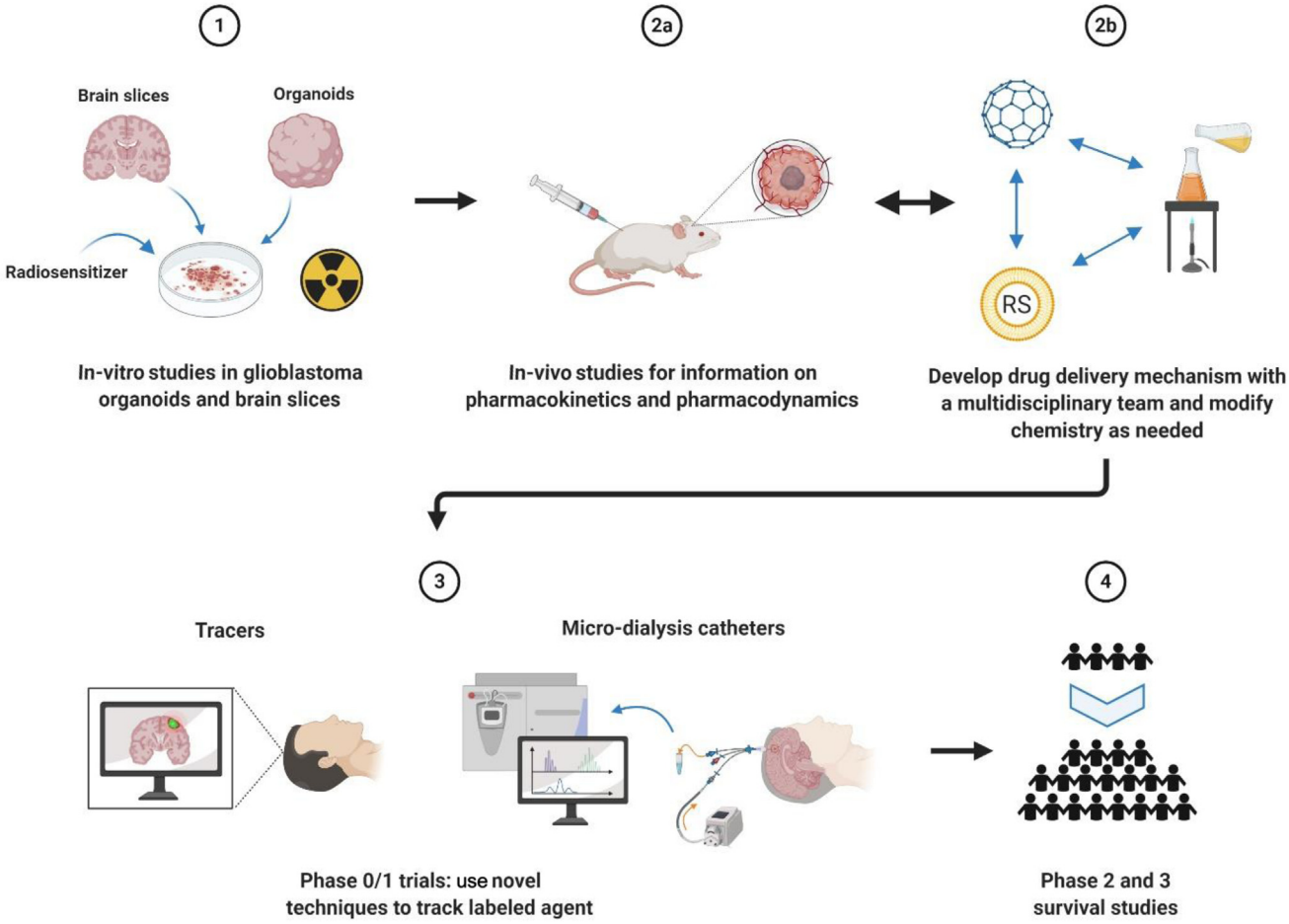

Figure 2. Proposed step-by-step strategy in developing radiosensitizers.

years in the study and control group, respectively (P = 0.61). Another randomized controlled trial[57] which included patients with metastatic brain tumors receiving bromodeoxyuridine with RT also failed to show any survival advantage over RT alone (OS, 4.3 vs. 6.12 months, respectively; P = 0.904).

Intravenous administration of iododeoxyuridine with RT was studied in 4 single-arm phase 1 and 2 trials.[59-62] An additional review reported survival data from trials using bromodeoxyuridine and iododeoxyuridine, as stated earlier.[53] A phase 1 trial conducted in patients with glioblastoma showed that the iododeoxyuridine was safe at therapeutic plasma levels.[60] However, 3 phase 2 trials[59,61,62] failed to show any major therapeutic benefit over historical data in patients with glioblastoma and AA, and at best, survival was comparable to historical data. OS ranged from 10.9 to 23 months.[53,59-62] PFS was reported to be 5.5 months in 1 trial.[60]

Adverse Events. Adverse events for bromodeoxyuridine were extensive. Bromodeoxyuridine had to be discontinued in 2 studies[54,55] in 20%–61% patients because of toxicities, including rash, leukopenia, increased alanine aminotransferase levels, and stomatitis. One study[50] concluded that bromodeoxyuridine has unacceptable neurotoxicity. Described adverse reactions included myelosuppression (1%–74%), nausea and vomiting (6%–67%), mucositis and stomatitis (5%–61%), skin toxicity (1%–57%), and neurologic toxicity (1%–19%).[50-58,63,64]

Iododeoxyuridine also presented with an array of adverse events. In 1 study with iododeoxyuridine, only 6% of the patients were able to complete full radiosensitizer infusion as planned, whereas 2 others reported withholding agent in 6%–23% of patients because of toxicities.[60-62] Among the reported adverse events across the studies hematologic toxicity (5%–27%) was the most prevalent.[53,59-62]

Valproic Acid

Mechanism of Action. Valproic acid (VPA), an established antiepileptic agent, acts by inhibiting histone deacetylase possibly by binding to the catalytic center of the enzyme. It reduces

glioblastoma cell survival and induces accumulation in the G2/M phase of the cell cycle in vitro. It also protects hippocampus-derived cells from radiation-induced cell killing in vitro.[65]

Clinical Evidence. A phase 2 trial consisting of patients with glioblastoma treated with VPA and RT determined that VPA with RT is tolerable in patients with glioblastoma. OS of 29.6 months and median PFS of 10.5 months were reported.[65]

Adverse Events. Toxicities attributed to VPA included hyperammonemia (7%) and mental status changes (10%).[65] The agent was discontinued in some patients because of mental status changes in conjunction with increased ammonia (5%) or increased amylase (3%) levels.[65]

Other

Additional radiosensitizers identified by our search included chloroquine, mibefradil dihydrochloride, pentoxifylline, *Serratia marcescens* extract, and 2-deoxy-D-glucose.

Chloroquine has been proposed to work by increasing oxidative stress induced by radiation. A double-blinded randomized phase 2 trial of oral chloroquine for the treatment of metastatic brain tumors showed no statistically significant benefit over the control group in terms of OS ($P = 0.839$), but an increased PFS was noted ($P = 0.046$). No additional adverse effects were reported in the treatment arm compared with adverse effects in the control arm.[66]

Pentoxifylline is a xanthine derivative that affects microcirculation and increases tissue oxygenation. A single-arm phase 2 study investigating oral pentoxifylline in patients with metastases to the brain concluded that the agent has low toxicity but does not seem to prolong survival compared with survival of patients in the RTOG trail (OS, 1.1 months; *P* value not reported).[67,68] Nausea and vomiting (28%), dizziness (28%), and headache (14%) were the more widely reported side effects in the study. Treatment was discontinued for 14% of patients because of toxicity.

Further studies investigated novel agents for use as radiosensitizers in patients with glioblastoma and AA. A phase 1 study[69] of oral mibefradil dihydrochloride, a T-type calcium channel blocker, established a positive safety profile for the agent. PFS and OS were 3 months and 9 months, respectively.

One study[70] investigated the safety and efficacy of subcutaneous injections of *Serratia marcescens* extract, which is believed to increase cytotoxicity in mononuclear cells without any clear mechanism of action as a radiosensitizer. Patients diagnosed with glioblastoma and AA tolerated the agent well, with a reported median PFS of 24 months and 2.75 months in patients with AA and glioblastoma, respectively, and OS of 33.75 months and 17.25 months in patients with AA and glioblastoma, respectively. The results were reported to be favorable compared with historical data, but no additional trials were found in our search to further investigate this. More frequently reported adverse events included infusion-related reactions (53%), chills (53%), headaches (27%), and back pain (20%).[70]

2-deoxy-D-glucose is a deoxymonosaccharide sugar that works as an inhibitor of glucose transport and glycolysis and also inhibits DNA damage repair after radiation. It was investigated in 2 separate phase 1/2 trials, one recruited patients with AA and glioblastoma[71] and the other with glioblastoma only.[72] Both studies reported a variety of side effects but determined that the agent was generally tolerable. Although the studies suggested encouraging survival data, no further trials investigating this were found in our search. Seizures, although less common, were reported in both studies (5%–10%) as an adverse event. In addition, nausea and vomiting (45%), diaphoresis (45%), mood/personality changes (70%), somnolence (83%), and intellectual deficit (83%) were reported between the 2 studies.[71,72]

DISCUSSION

Surgical resection and radiation are the mainstay treatment of malignant brain tumors. However, the hypoxic core of tumors provides a protective function to these cells from therapeutic ionizing radiation that depends on oxygen for the generation of free radicals to induce cell death. In this systematic review, we have gathered the most comprehensive resource on clinical studies of nonantineoplastic radiosensitizers for primary and metastatic CNS tumors to date. Our review found 15 unique classes of radiosensitizers, with 22 radiosensitizing agents that have been assessed in clinical trials, among which only 2 showed limited efficacy in improving OS: efaproxiral, and fluosol with oxygen. Through an analysis of their mechanism of action and their clinical efficacy and safety profile, it is clear that better strategies are needed to design and implement the ideal radiosensitizer.

The challenges limiting radiosensitizers are multifaceted. Although many agents have been tested in vitro, our limited understanding of their pharmacokinetic and pharmacodynamic features in human patients can significantly affect dosing regimens and safety profiles. Agents identified in our review were delivered orally, intravenously, intra-arterially, or via inhalation. Considering the narrow range of substances that can cross the blood-brain barrier, getting agents to the tumor site is a significant hurdle. Although the 2 agents of limited efficacy in our review did not require traversing of the blood-brain barrier to exert their influence, we recommend that early experimental designs focus on biological proof-of-concept, showing directly or indirectly that the putative mechanism of action is replicated in the native tumor microenvironment as well. These microenvironments can be simulated in organoids, which can model intratumoral heterogeneity and spheroids, as well as organotypic brain slices (step 1, **Figure 2**).[73,74] Organoids have already been used in testing therapeutics. Recently, Jacob et al.[75] described an effective method of generating patient-derived glioblastoma organoids that maintained heterogeneity of parental tumors. These organoids were also successfully xenografted into mice with aggressive infiltration. This reliable method for reproducing glioblastoma organoids, in vivo and in vitro, serves as a prime modality for radiosensitizer study. Adapting them as models for radiosensitizer assessment may yield more accurate tumor response data.

Delivery mechanism can be modified in conjunction to in vivo studies, gathering information on pharmacokinetics and pharmacodynamics (steps 2a and 2b, **Figure 2**). These methods include, but are not limited to, physiologic approaches such as binding radiosensitizers to endogenous ligands with established receptors on the blood-brain barrier, pharmacologic approaches such as modifying molecular size and charge, and nanoparticle-based approaches using liposomes.[76]

Because one of the potential targets of radiosensitization is tumor oxygenation, direct assessments of tumor response in early clinical trials can include sampling of the tissue oxygen concentration, such as with microdialysis catheters, or assessment of posttreatment tissue for markers of hypoxia, such as CA-9. A decrease in hypoxia markers can be expected and potentially used as a response marker. Indirect assessments can include advanced imaging modalities (step 3, Figure 2), such as radio-labeled radiosensitizers. Fluorescent hypoxia probes can also provide valuable efficacy data. Various fluorescent probes have been described in the literature for detecting hypoxia in vivo by means of measuring nitroreductase activity, an enzyme that is increased in hypoxia.[77,78] Clinically, positron emission tomography imaging using [^{18}F]fluoromisodazole, a hypoxia radiotracer, has been used, which may serve as a tool for radiosensitizer assessment.[79] Positive outcomes in these steps can warrant large-scale clinical trials assessing survival outcomes and QoL. A radiosensitizer development framework using the suggested protocol is shown in Figure 2.

Nine agents had overlapping therapeutic and toxicity windows with participants requiring dose or schedule adjustment because of systemic toxicity.[15,22,29,45,54,55,60-62,65,68,72] Although detailed knowledge of the pharmacokinetics of each study agent can be of great value, local delivery of agents may be another consideration for bypassing systemic metabolism and the blood-brain barrier. Targeted delivery mechanisms such as nanoparticle-based radiosensitizers may increase radiotherapeutic ratio, decreasing the adverse effects on normal tissues.[80] This research necessitates multidisciplinary collaboration with surgical neuro-oncologists.

Study Limitations

Our review should be considered with some limitations. Although we cast a wide net to include all relevant reported trials using radiosensitizers, it is possible that our search would have missed some studies. There is a possibility of publication bias if reports of unsuccessful agents were not published. Our review did not include agents that have established nonantineoplastic roles, and it is possible that they may act synergistically with radiation as radiosensitizers. Furthermore, the variation in treatment regimen and heterogeneity in patient population and tumor type prevented us from conducting a pooled analysis. This limitation also means that the presented data should be interpreted with caution because a combination of tumor types with widely different survivals were included in the calculation of OS and PFS. The adverse events may be a result of the complete treatment regimen and may not necessarily reflect the adverse effects of the radiosensitizer alone.

CONCLUSIONS

Radiosensitizers can be a promising approach to addressing the decades-long issue of brain tumor outcomes and can emerge as a standard of treatment if approached methodically. Because of the limited successes achieved, innovative strategies such as drug repurposing or synthetic approaches may be needed. Preclinical studies should establish the efficacy of drugs in vitro along with target dosage. To this front, model systems that emulate tumor microenvironment may be used. The ability of the agent to penetrate to the hypoxic core of the tumor may be simulated using glioblastoma explant cultures or organoids,[81] with strategies to ensure that the study agent colocalizes with hypoxic regions. Further steps in animal models need to establish the ability of the agent to cross the blood-brain barrier and its presence in tumor cells before agents are taken to clinical trial. Using newer technology to overcome the hurdles of past generations of radiosensitizers may prove to be fruitful.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Usman Beg: Methodology, Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing, Supervision, Visualization, Project administration. **Brianna Michelle Snyder:** Validation, Investigation, Data curation, Writing - original draft. **Sarosh Irfan Madhani:** Validation, Investigation, Data curation, Writing - original draft. **Nima Hamidi:** Validation, Writing - review & editing, Visualization. **Varun Padmanaban:** Writing - review & editing. **Leonard C. Tuanquin:** Writing - review & editing. **Timothy J. Kruser:** Writing - review & editing. **James Connor:** Writing - review & editing. **Alireza Mansouri:** Conceptualization, Methodology, Validation, Writing - original draft, Writing - review & editing, Supervision, Visualization, Project administration.

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SUPPLEMENTARY DATA

Supplementary Table 1. Search Strategy

Database	Search Term (1)		Search Term (2)
Web of Science	Radiosensitizer* OR Radiation sensitiz* agent OR Radiation sensitiz* drug	AND	Brain cancer OR Brain tumo*r OR Brain radiation
PubMed	Radiosensitizer OR "Radiation-Sensitizing Agents"[Mesh] OR "Radiation-Sensitizing Agents"[Pharmacological Action] OR Radiation sensitizing agent OR Radiation sensitizing drug	AND	"Brain neoplasms"[MeSH Terms] OR Brain cancer OR Brain metastasis OR Brain metastases OR Brain tumor OR Brain radiation
Cochrane	Radiosensitizer* OR Radiation sensitiz* OR Radiation sensitiz* agent OR Radiation sensitiz* drug	AND	Brain neoplasm OR Brain cancer OR Brain metastas* OR Brain tumo#r OR Brain radiation
Embase	"Radiosensitizer?" OR "Radiosensitizing agents"/exp OR "Radiation sensitizing" OR Radiation sensitizer* OR Radiation sensitiz* agent OR Radiation sensitiz* drug	AND	Brain cancer OR "Brain cancer"/exp OR Brain metastas* OR Brain tumo?r