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e-ISSN 2083–4640
ISSN 1507–1367

REVIEW ARTICLE

Reports of Practical Oncology and Radiotherapy
2025, Volume 30, Number 2, pages: 269–281
DOI: 10.5603/rpor.105654
Submitted: 13.01.2025
Accepted: 02.04.2025

New approaches to overcome radioresistance in glioblastoma: mechanisms, targets and role of innovative therapies, new particles and non-photon radiotherapy in 2024. A systematic review

Kamel Debbi[1, 2]*, Gokoulakrichenane Loganadane[1]*, Nhuhanh To[1, 2], Mohamed Aziz Cherif[1], Chahrazed Boukhobza[1], Hanan Rida[1], Noémie Grellier[1], Hamid Mammar[3, 4], Yazid Belkacemi[1, 2]

On behalf of AROME (Association of Radiotherapy and Oncology of the Mediterranean Area; www.aromecancer.org) and Transatlantic Radiation Oncology Network (TRONE)

[1]AP-HP, Department of Radiation Oncology and Henri Mondor Breast Center, Henri Mondor University Hospital, University of Paris Est Creteil (UPEC), France
[2]Institut Mondor de Recherche Biomédicale (IMRB), INSERM U955, i-Biot, UPEC, Créteil, France
[3]Department of Radiation Oncology, Proton Therapy Centre, Curie Institute, Orsay, France
[4]Department of Radiation Oncology, Curie Institute, Paris, France
*These authors contributed equally to this work.

ABSTRACT

Glioblastoma (GBM) is the most prevalent and deadliest form of primary malignant brain tumor in adults. Radiation associated with chemotherapy following maximal feasible surgery is the standard of care. However, it remains an incurable disease with inexorable recurrence after multimodal therapy due to several factors including tumor aggressiveness with high degree of tumor cell infiltration into surrounding brain tissue, high proliferation, molecular heterogeneity and radioresistance. A better understanding of the tumor biology may allow development of new strategies to overcome treatment resistance.

Overcoming radioresistance in GBM has been considered as a challenge for decades. In this systematic review we aim to summarize biologic pathways and mechanisms of therapeutic resistance involved in GBM and try to define some potential future therapeutic perspectives. The main mechanisms of radioresistance that we will discuss are hypoxia, the subpopulation of cancer stem cells in GBM, and the epidermal growth factor receptor (EGFR) expression. We will also focus on the potential role of innovative approaches, such as targeted therapy, nanoparticles and non-photon radiotherapy.

Keywords: glioblastoma multiforme; brain tumors; molecular pathways; radioresistance, nanoparticles, proton therapy

Rep Pract Oncol Radiother 2025;30(2):269–281

Address for correspondence: Yazid Belkacemi, MD, PhD, Department of Radiation Oncology and Henri Mondor Breast Center. Henri Mondor University Hospital, 51 avenue Mal de Lattre-de-Tassigny, Créteil. 94000, France, tel: (+33) 1 49 81 45 22, fax: +33 1 49 81 25 89; e-mail: yazid.belkacemi@aphp.fr

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Introduction

Glioblastoma (GBM) is the most prevalent and the deadliest form of primary brain malignancy in adults. The incidence is around 5 per 100,000 in the United States and Europe [1]. The 2016 World Health Organization (WHO) classification for central nervous system tumors incorporated molecular information into the diagnosis of brain tumors for the first time, breaking with the conventional histogenetic classification. Compared with the 2016 scheme, the new 2021 WHO classification incorporates more molecular alterations into the diagnosis [2].

The standard of care in GBM is based on maximal safe surgery whenever possible, radiation therapy and chemotherapy (CT). The addition of CT to radiation resulted in improved median overall survival from 12.1 to 14.6 months in the landmark Stupp study [3]. Although the tumor may well respond initially to multimodal therapy, inexorable recurrence occurs. A better understanding of the tumor biology may allow development of new strategies to overcome treatment resistance. Indeed, some alterations are related to constitutive activation or suppression of cellular signal transduction pathways potentially leading to radiation and/or chemotherapy resistance [3, 4]. Recognizing the underlying biologic processes involved in resistance can allow potential targets identification for a better therapeutic ratio.

In this systematic review we aim to explore the current scientific literature of potential mechanisms involved in radioresistance of GBM and potential ways to reverse it.

Methods

The available literature on GBM was searched using the MEDLINE database and PubMed from 1987 to 2023 using the following keywords: "glioblastoma, radioresistance, nanoparticle therapy, proton beam therapy, carbon beam therapy" (Fig. 1). Additionally, prominent authors related to the field, as well as citations from landmark studies, were further searched and studied. There is an emphasis on GBM in this systematic review, as the majority of papers on the topic of brain tumor radioresistance have been specific for GBM.

Initially, 1693 articles were available. Based on the abstract, 1202 were excluded. Thus, we were left with 491 articles. We then selected 115 references that were the most cited. 26 articles were ultimately excluded due to repeated data.

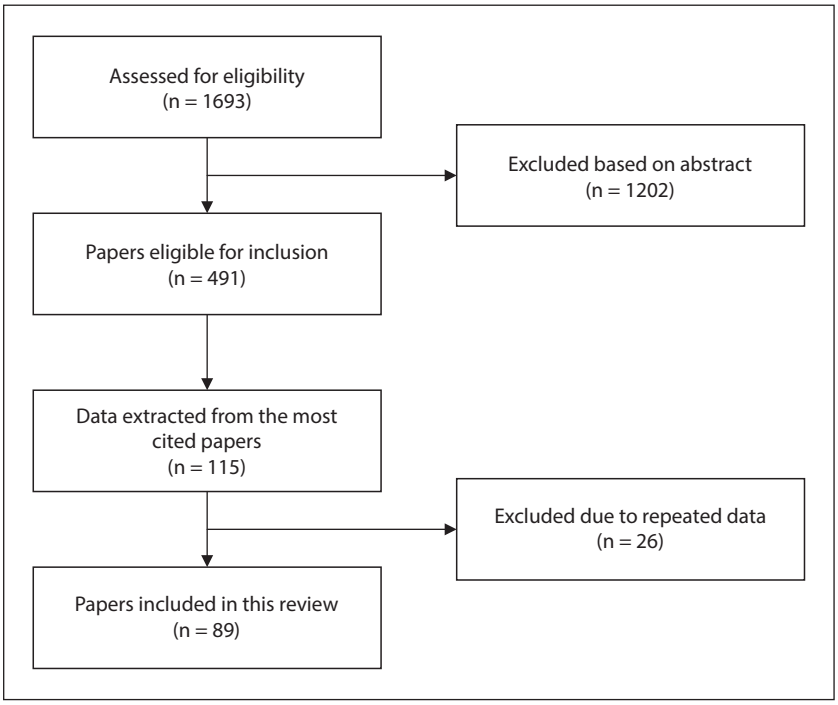


Figure 1. Article selection process according to PRISMA

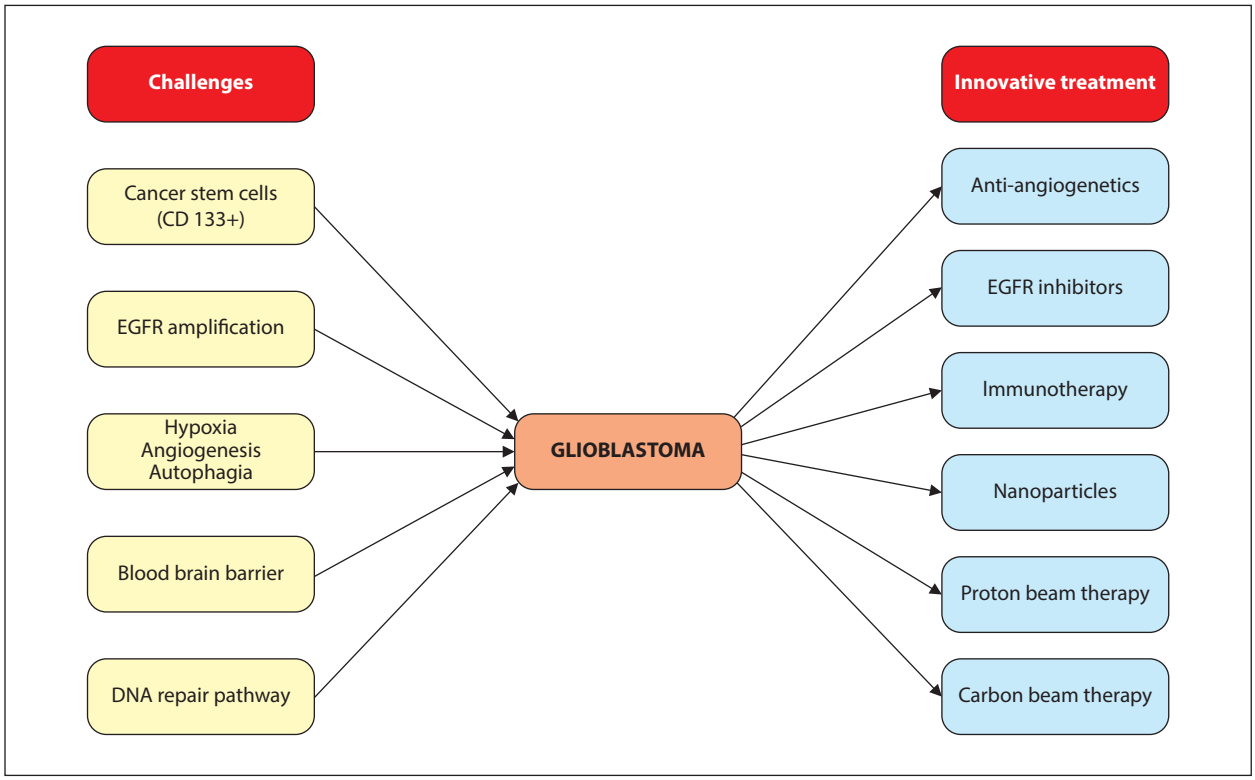


Figure 2. Overview of resistance mechanisms and innovative treatments in glioblastoma

Therefore, 89 papers were included in this systematic review.

Tumor biology to overcome radioresistance of glioblastoma

Mechanisms of radioresistance

Mechanisms of radioresistance is presented in Figure 2.

Cancer stem cells and radioresistance

Numerous studies have identified a key subpopulation of cancer stem cells (CSC) in GBM that have properties similar to the normal stem cells [5]. Intratumoral heterogeneity and therapy resistance are believed to be promoted by the self-renewal and differentiation of GBM stem cells that can survive in unfavorable and complex hypoxic microenvironments, especially for advanced tumors. Typically, CSCs promote increased invasiveness through epithelial mesenchymal transformation and facilitate neovascularization when cellular growth exceeds the vascular supply. An interesting theory is that GBM CSCs migrate with underlying driver mutations at the subventricular zone along ventricles and are capable of migrating away from the subventricular zones into the deeper brain regions and mutate further to develop glioma [6].

One of the main approaches to recognize CSCs was to identify specific glycans attached to proteins or lipids on the cell surface that are more common than normal tissue. The most used biomarkers include CD133, CD44, CD15, CD24, CD90, CD49f, CXCR4, L1CAM and ABC efflux transporters. CD133 represents an important biomarker used to identify the CSC population within various tumor types and may have a role in cell growth, proliferation and pathophysiology of growing tumors [7]. The stemness of CD133+ cells was shown by its ability to generate neurospheres in vitro and induce tumor formation in *in vivo* models [8].

Radioresistance is considered to be mediated, in part, by a population of cancer stem cells expressing CD133 marker [9, 10]. A study from *in vitro* model by Bao et al. showed that $CD133^{+}$ cells were more resistant to X-ray exposure than $CD133^{-}$ cells [11]. They also reported higher levels of active deoxyribonucleic acid (DNA) damage proteins (especially involved in double-strand repair) such as ATM, Chk1, and Chk2,

in the $CD133^+$ population, suggesting that represents one of the mechanisms of radioresistance in $CD133^+$ cells. In irradiated xenografts taken from brain samples, less DNA damage foci were found in $CD133^+$ cells compared to $CD133^-$, suggesting that $CD133^+$cells, indeed do have a greater capacity to repair DNA [12]. While $CD133^+$ cells may have roughly the same number of double-stranded breaks as the $CD133^-$ cells, the number of foci may differ because the DNA repair machinery was more active in preventing fusion of the DNA break sites in the $CD133^+$ population. Upregulated expression of genes involved in the embryogenesis (such as *HOX*) was found in $CD133^+$ GBM cells and was correlated with worse survival in the clinical series of 42 GBM patients [13].

EGFR expression and radioresistance

The epidermal growth factor receptor (EGFR) expression seems to play a key role in radioresistant stem cells profiles and may be crucial for development of new therapeutic approaches. High EGFR expression, related to gene amplification but not the constitutively active mutant EGFRvIII, is correlated with poor survival. Murat et al. suggested that forcing differentiation of these radioresistant stem-like cells could be a therapeutic strategy [13]. Such evidence supports the role of stem cell behavior in mediating radioresistance.

Hypoxia and radioresistance

Hypoxia has not been well studied as a factor of radioresistance in GBM. Hypoxia has been suspected to have a role in maintaining cancer stem cell niches because of their pro-angiogenic and stem cell-enhancing activities. A study of human bone marrow progenitor cells found that in hypoxic conditions, these cells had upregulated expression of angiogenic markers and secreted more vascular endothelial growth factor (VEGF) [10, 14]. Furthermore, another study found that hypoxic conditions prevented human embryonic stem cells from differentiating [15]. Hypoxia drives many mechanisms involved in cancer progression and treatment resistance and an increased risk of death.

Potential targets of radioresistance

Main trials on potential targets of radioresistance in glioblastoma are presented in Table 1 and Figure 2.

Angiogenesis as a target

Angiogenesis is known to promote tumor growth and aggressiveness [16], and the signaling

Table 1. Main trials on potential targets of radioresistance in glioblastoma (GBM)

	Authors	Type of study	Year	Protocol	Number of patients	Results	References
Angiogenesis	Friedman et al.	Phase 2	2009	Bevacizumab alone *vs.* bevacizumab with irinotecan	167	PFS : 4.2 *vs.* 5.6 months OS: 9.2 *vs.* 8.7 months	[28]
	Hainsworth et al.	Phase 2	2012	Surgery: radiation therapy + temozolomide + bevacizumab Adjuvant bevacizumab + everolimus	68	PFS: 11.3 months OS: 13.9 months	[30]
	Chinot et al.	Phase 3	2014	Adjuvant temozolomide *vs.* adjuvant temozolomide + bevacizumab	458	PFS: 6.2 *vs.* 10.6 months OS: 66.3% *vs.* 72.4% at 1 year	[31]
Upregulate growth pathways	Sathornsumetee et al.	Phase 2	2010	Bevacizumab + erlotinib in GBM or anaplastic glioma (AG)	57	PFS: 28% *vs.* 44% at 6 months	[52]
Autophagy	Galanis et al.	Phase 2	2005	Temsirolimus in recurrent GBM	65	PFS: 7.8% at 6 months OS: 4.4 months	[55]

Table 1. Main trials on potential targets of radioresistance in glioblastoma (GBM)

	Authors	Type of study	Year	Protocol	Number of patients	Results	References
Immunotherapy	Reardon et al.	Phase 3	2020	Nivolumab *vs.* bevacizumab	369	OS: 9.8 *vs.* 10.0 months Objective response: 7.8% *vs.* 23.1%	[59]
	Weller et al.	Phase 3	2017	Rindopepimut + temozolomide *vs.* temozolomide alone	745	OS: 20.1 *vs.* 20.0 months	[61]

PFS — progression-free survival; OS — overall survival

pathways that regulate it have been well studied. The VEGF receptor family is one of the main components of angiogenesis. Macrophages secreting angiogenic factors are recruited by VEGFR1 [17]. However, VEGFR1's role in angiogenesis appears to be complex, as one of its ligands, Flt-1, has been found to inhibit angiogenesis in some tissues, such as the eye, yet promote vascularization in gliomas [18, 19]. VEGFR2 promotes endothelial cell proliferation via the RAS pathway, migration, and permeabilization, allowing for leukocyte extravasation [20–22]. VEGFR3 is critical for the normal development of lymphatic vessels and in very rare cases, can contribute to lymph node metastasis of brain tumors [23, 24].

One study has shown that GBM has particularly high angiogenic activity compared to other tumor cell lines, and the antiangiogenic drug bevacizumab (monoclonal antibody targeting VEGF A) has been shown to be more effective against tumor cell types with higher angiogenic activity, including GBM [25]. However, there is a need to validate that *in vivo* for glioblastomas that are among the more angiogenic tumors. Studies *in vitro* on GBM cell lines have investigated the effects of that combining radiation with VEGFR inhibitors. Two studies showed that VEGFR inhibitor SU5416 decreases microvessel density and delays tumor growth in mice [26–28]. In 2009, a pivotal phase II clinical trial of 167 patients demonstrated the efficacy of the anti-angiogenic drug bevacizumab against recurrent GBM [28]. Bevacizumab was approved by the FDA for recurrent GBM in 2009 [29]. Combination therapies with bevacizumab have been examined for effectiveness in prolonging survival in recurrent glioblastoma. Bevacizumab alone is only mildly less effective than combination therapy with irinotecan (median progression-free survival (PFS) rates were 4.2 and 5.6 months, respectively) [28]. In addition, a double drug regimen of temozolomide and bevacizumab plus radiotherapy yielded a median overall survival (OS) of 13.9 months and a median PFS of 11.3 months [30]. The study concluded that their strategy was encouraging, but whether bevacizumab sensitizes tumor cells to radiation has yet to be studied. This was true until the two recent randomized results. In their phase III, Chinot et al. showed that the addition of bevacizumab to standard radiotherapy–temozolomide for newly diagnosed glioblastoma improved PFS but not OS. Quality of life and performance status remained unchanged but the rate of toxicities was significantly higher with bevacizumab than with placebo [31]. The second study by Gilbert et al. found the same results as the first study [6]. However, both studies did not analyze the VEGF and VEGFR2 polymorphism status that are considered highly prognostic.

MGMT as a chemotherapy target

MGMT, a DNA repair protein, appears to be upregulated in a subpopulation of cancer stem cells expressing CD133 which may confer resistance to systemic therapy and radiotherapy [32]. Temozolomide, a chemotherapeutic DNA alkylating agent, induces a DNA mismatch between guanine and thymidine. MGMT can reverse this DNA alkylation to repair DNA. $CD133^{+}$ cells seem to have less MGMT gene promoter methylation, allowing expression of MGMT [33]. Higher MGMT promoter methylation has been correlated with improved survival and increased responsiveness to radiotherapy in GBM patients [33–35]. It was also found that intensifying the dose of temozolomide increases the survival only for patients with MGMT methylation suggesting that temozolomide is not necessary for patients without methylation [33].

In patients with low MGMT expression, the temozolomide may cause longer-lasting DNA damage that, when combined with radiation-induced DNA breaks, is more lethal to tumor cells [34].

Upregulated growth pathways

EGFR is either highly expressed or constitutively active in up to 50% of GBM. The high expression of EGFR is due to gene amplification, and the constitutively active form of EGFR (EGFRvIII) lacks the extracellular ligand-binding domain [35, 36]. Downstream of EGFR involves the Ras/Raf/Mef/Erk, Ras/PI3K/Akt, PKC, JAKs, and SRC pathways [37]. In addition, VEGFR appears to be upregulated following EGFR activation as well [38]. These pathways promote cell growth and proliferation, suggesting that EGFR pathways could contribute to resistance to cell death by irradiation. By itself, EGFR promotes tumor growth [39, 40]. Gene amplification and the presence of a mutant EGFRvIII, however, do not account for higher EGFR expression in GBM cells. A study found that EGFR-high cells gave rise to both EGFR-high and EGFR-low cells [41]. A possible explanation is that epigenetic mechanisms modulate EGFR expression. When GBM cells were exposed to a demethylation agent, EGFR expression increased. When GBM cells were treated with an inhibitor of histone deacetylation, EGFR expression decreased [42].

In a mouse model preclinical study, administration of an EGFR (and VEGFR) inhibitor, ZD6474, delayed growth of lung cancer *in vivo* [43]. Then, it was found that treating epidermoid carcinoma xenografts in mice with C225 (anti-EGFR monoclonal antibody) before and after radiation improved tumor necrosis and inhibited tumor angiogenesis [44]. Furthermore, a subsequent paper demonstrated the causal relationship between EGFR expression and cancer radioresistance [45]. Compared to EGFR-low cells, EGFR-high cells required a higher dose of radiation to be killed. Irradiation also appeared to increase the expression of EGFR and downstream targets like cyclin D1 in EGFR-high cells.

Preclinical studies have shown that treating non-small cell lung cancers, epidermoid carcinomas, as well as colon and lung cancers with EGFR inhibitors can improve radiosensitivity. Erlotinib, an EGFR inhibitor, appears to be a promising radiosensitizer in oncology [46–49]. In a study on head and neck cancer cell lines, it was found that erlotinib could reverse several mechanisms of radioresistance, such as repopulation, anti-apoptotic mechanisms, EGFR activation, and DNA repair [50]. Respectively, in combination with ionizing radiation, erlotinib reduced the fraction of cells in the S phase, increased apoptosis, reduced radiation-induced EGFR autophosphorylation, and reduced expression of Rad51, which is a DNA repair protein. Nevertheless, EGFR gene amplification was not predictive of increased radiosensitivity when associated with Erlotinib. A study of an orthotopic xenograft model found that EGFR-amplified GBM possessing amplified copies of EGFR showed varying sensitivities to radiation. However, in that study, treating GBM with radiation and erlotinib prolonged survival in the more aggressive radiation regimen (20 Gy/5 days versus 12 Gy/12 days). In other words, erlotinib appears to be an effective radiosensitizer combined with intensified radiation in mice. Clinical trials of erlotinib and radiotherapy combined are underway. A trial has yet to be done for GBM or other brain tumors. Previous evidence of erlotinib in humans has been promising. A phase II trial combining bevacizumab with erlotinib found that a combination of drugs improved PFS compared to bevacizumab alone in brain tumors. Although, they found that erlotinib was somewhat toxic, as 93% of their patients developed a rash (54% grades 1 or 2, 39% grade 3) [51]. Preclinical studies of the interaction between EGFR and VEGFR inhibitors will be necessary to alleviate drug toxicity [52].

Hypoxia as a target

Adding to the evidence of cancer stem cells conferring radioresistance, Zhizhong et al. found HIF-2α expression in GBM stem cells positive for CD133. Expression of HIF-2α correlated with poor patient survival [53]. Pistollato et al. found the same correlation of HIF-2α expression with $CD133^+$ cells [33]. Furthermore, they identified that these cells localized to the inner core of the GBM, and that moving outwards to the periphery, HIF-2α expression decreased in a gradient. Moreover, they found that this hypoxic gradient was correlated with the MGMT expression gradient. In sum, hypoxic, $CD133^+$ cells express MGMT at higher levels and seem to localize to the inner core of the GBM.

Autophagy as a target

Cellular autophagy, induced by rapamycin (mTOR inhibitor), appears to suppress DNA repair and stimulate differentiation in glioblastoma stem cells [54]. Rapamycin induces autophagy by forming a complex with enzyme FKBP-12, inhibiting mTOR and thus its downstream targets [55]. These cellular consequences of autophagy were then thought to confer radiosensitivity. When rapamycin was given in conjunction with irradiation to mice bearing gliomas, their survival was prolonged compared to irradiation-only mice [53]. Irradiation alone does not cause GBM stem cells to differentiate, but in combination with rapamycin, it does cause the stem-like cells to differentiate [55]. It has not been resolved whether irradiation induces cellular autophagy in glioblastoma stem cells or has no effect. These experiments need to be repeated to reach any relevant conclusion. Rapamycin reached clinical studies, yet phase II trials showed minimal efficacy in recurrent glioblastoma. Rapamycin was given as its ester analog, temsirolimus (CCI-779), with the same mTOR inhibitory activity but improved aqueous solubility [56]. Half of the patients had Grade 3 or higher non-hematologic toxicity, and after six months, only 7.8% of patients were alive and without the disease. Another nearly identical phase II trial demonstrated that 1 patient out of 43 was progression-free after six months and that the median time to progression (TTP) was 2 months [57]. Induction of autophagy may still be a potential radiosensitizing method, but a less toxic and more effective compound has to be found.

Innovative therapies to overcome radioresistance of glioblastoma

Immunotherapy

Immunotherapy is a therapeutic approach consisting in stimulating the natural immune system to target tumor. Antibodies targeting cytotoxic T lymphocytic antigen 4 (CTLA4) and programmed death cell 1 (PD1) and programmed death cell ligand 1 (PDL1) have made great breakthroughs over the last decade and transformed the cancer therapy landscape. Many obstacles that potentially hamper the effectiveness of immunotherapy are present in the context of glioblastoma. Glioblastoma is immunologically cold with low mutational burden, low number infiltrating T cells and low PD1/PDL-1 expression [58]. The heterogeneous tumor profile facilitates escape from immunosurveillance.

Recently, a phase III compared nivolumab (PD1 inhibitor) to bevacizumab, the standard of care for recurrent glioblastoma. The trial failed to meet the primary endpoint of OS. The objective response rate and PFS were significantly inferior with nivolumab compared to bevacizumab. However, an interesting finding is that 8% of patients who had a response to nivolumab had a median response duration of 11.1 months versus 5.5 months for 23% who responded to bevacizumab [59]. There is a need to develop biomarkers to predict response to immunotherapy.

Several phase I and II trials are currently investigating the role of a combination of immunotherapy with radiation [60]. Another immunotherapy approach is based on vaccines targeting tumor-specific antigens. The EGFRvIII amplifications which is present in 25–30% was one of the most promising targets. Despite phase II trials showing an encouraging response, Phase III trial of EGFRvIII vaccine terminated early due to lack of improvement in overall survival [61].

Chimeric antigen receptor T-cell therapy (CAR-T) cell therapy is a new immunotherapy approach in oncology, currently approved in hematologic malignancies. CAR-T cells are autologous or allogeneic modified T cells with extracellular domains recognizing a specific tumor-related antigen and the intracellular domain capable of inducing a T cell response signal. These modified T cells are then reinjected into the patient, where they can induce targeted killing of cells containing the associated tumor antigen. The tumor antigens that have been most investigated for CAR targets in glioblastoma are EGFRvIII, IL-13Ra2 and Her2. A recent study reported the feasibility and encouraging results with $CD133^{+}$ directed CART in orthotopic glioblastoma xenograft models [62].

Role of protons beams

Ionizing radiation (photons or charged particles) can create at the cellular level an ionized water molecule ($H_2O^{+\bullet}$) which interact with other water molecules to form hydroxyl radicals ($^{\bullet}OH$). The initially ejected electrons (e^{-}) possessing sufficient energy are able, in turn, to cause further ionizations until their energy is totally dissipated to create an aqueous electron (e^{aq}) and may generate reactive spe-

cies (hydrogen atoms (H•) or superoxide (O2•) by combining with other species. Ionizing radiation is considered a non-discriminatory process since all molecular species may be damaged in a cell. However, DNA is the main molecular target for the damaging effects of ionizing radiation in cells. The indirect effect involves ˙OH radicals which are known to be highly reactive (together with less reactive reducing species they may damage DNA) and is the predominant mechanism for low linear energy transfer (LET) ionizing radiations (X-rays and δ-rays and proton at high energy). The direct effect consists in DNA bases damage directly induced by radiation.

DNA double-strand break (DSB) represents the most critical damage for the lethal effects of radiation. While both direct and indirect effects cause DNA damage, it was suggested that only indirect events occurring 2 nm within the DNA produce multiple chain reactions called multiply damaged sites (MDS) that are irreparable [17].

The spatial distribution of charged particles in tissue is entirely different to those of photons (x- and gamma rays). The track structure produces a radial dose distribution around the proton trajectory, with more ionizations and more indirect MDS [63, 64].

A well-localized dose deposit (Bragg peak) at the end of the particle trajectory, the absence of dose beyond the particle range and a steep dose gradient with sharp lateral penumbra allow a highly conformal dose distribution to the target volume with sparing of normal tissues [65]. Such beams can therefore maximize the ratio of tumor-to-normal-tissue dose and improve the therapeutic ratio compared with conventional photon therapy [66].

Petr et al. showed from a series of 47 patients treated for GBM that the use of proton beam therapy with temozolomide (n = 16), instead of photon therapy, reduced considerably the loss of gray and white matter compared to the association of temozolomide with photon-therapy [three-dimensional conformal radiotherapy (n = 27); intensity-modulated radiation therapy (n = 24)]. Brain-tissue volume changes were strongly correlated with the radiation dose delivered to the healthy brain [67].

Kong et al. reported an OS and PFS rates at 18 months of 61% and 42.7% in 24 patients treated for GBM with proton beam therapy according to the standard Stupp protocol after total resection [proton therapy: 60 Gy relative biological effectiveness (RBE) in 30 fractions; with concurrent oral temozolomide at 75 mg/m^2, continuously for 6 weeks, followed by at least 6 cycles of adjuvant chemotherapy at 150 to 200 mg/m^2 for 5 days during each 28-day cycle] [68, 70]. Proton beam radiotherapy allowed a marked improvement in the levels of OS and PFS compared to the results reported by Stupp et al. in 2005 [69, 71]. Matsuda et al. on a series of 48 patients treated for GBM, reported an OS rate of 36.9 months *vs*. 26.2 months for the group treated with proton therapy (hyperfractionated with concomitant boost) (n = 17) at the total dose of 96.6Gy RBE compared to the group treated with conventional photon therapy (n = 31) at the total dose of 60 Gy in 30 fractions [70].

Mohan et al. in a randomized phase II trial showed that patients with GBM treated with proton beam therapy had lower doses to the healthy brain compared to patients treated with photon therapy and experienced less grade 3 lymphopenia [71]. A recent review reported similar rates of local control and overall survival [72].

Combined radiotherapy and nanoparticles

Nanoparticles (NPs) are defined as objects typically on the scale of 1–100 nm in diameter [73]. The concept of potentiation of the effect of ionizing radiation (IR) by the presence of high Z materials at the intracellular level was first described by Santos Mello et al. in 1983. These authors have shown in mice that the interaction of Iodine (injected intra-tumoral) with IR increased cell death by 85% [74]. NPs injected intravenously reach tumor through abnormal and permeable tumor vasculature, with large pores (Ø = 0.1–3 μm), abnormal pericytes and get trapped in the tumor bed due to reduced lymphatic circulation. This selective delivery of NPs in tumors is called the enhanced permeability and retention effect (EPR) [75–79].

In the presence of NPs, the interaction with the IR beam (charged or uncharged particles) and secondary particles (photons and electrons) produced along their trajectory with the high-Z constituent atoms of nanoparticles lead to a cascade of ionizations resulting in the enhancement of the radiation effect even in cases when NPs are considered as nano-radio-enhancers (NREs) [80].

High-Z NPs are generally good radiosensitizers due to their ability to antagonize repair mechanisms of DNA lesions in the S phase cell (the most radioresistant) by downregulating repair proteins such as thymidylate synthase (important for DNA damage repair) [81].

Also, nanoparticles with high atomic Z will improve the RBE proton beam by 15% to 20%, the LET proton beam by 25 to 40% and the ratio-enhancement effect was found to be increased at the end of the ion track [82, 83]. However, physical and chemical mechanisms involved in the dose enhancement in the vicinity of Nps are not fully understood. In the near future, new Monte Carlo-based (Geant4-DNA) simulations, providing the computation of local energy transfers and chemical species production yields, may help to reduce these uncertainties [84].

Role of carbon beams

Similarly to Protons, Carbon ions interact with the tissue and deposit maximal energy near the end of their variation (Bragg peak). As a consequence, the lateral dose gradient around the target volume is faster for a carbon ion when compared to a proton. Beyond the peak, almost no dose is delivered. However, a small fraction of primary carbon ions can undergo interactions with the tissue associated with nuclear fragmentation involving lower atomic number particles, generating a cluster beyond the peak tail.

Interestingly, LET and energy beam range (EBR) rise steadily with increasing depth for carbon ions until reaching the maximum in the peak region corresponding to the tumor. Moreover, carbon ions are associated with the highest RBE ratio (peak/plateau) and offer the best balance in terms of physical dose distribution and biological effects. Carbon ions also possess potential radiobiological advantages such as: (1) decreased oxygen enhancement ratio (OER), which is well suited for photon-resistant, hypoxic tumours; (2) reduced repair capacity; (3) decreased cell-cycle dependence; and (4) potentially higher immunological responses related to the predominance of double-strand DNA damage [85].

Few therapeutic results on GBM have been reported with carbon ions. Mizoe et al. reported a median survival of 17 months in patients who received a dose of 50 Gy in photons followed by supplementary dose 16.8–24.8 Gy RBE in 8 fractions with a carbon beam over 2 weeks [86].

Eberle et al. published their reirradiation experience with carbon ion beams in 27 patients with recurrent glioblastoma (dose delivered: 45 Gy RBE/15 fractions). The median LC time after reirradiation completion was 7 months (range: 2–23 months) with LC rates were 45% and 30%, at 6- and 12-month, respectively. The median OS reported was 12 months (range: 3–25) [87]. Kaul et al. from their retrospective cohort of 133 patients reirradiated for recurrent GBM, showed an overall survival rate of 6 months (with fractionation schemes of 41.8 Gy RBE/3.8 Gy RBE and 49.4 Gy RBE/3.8 Gy RBE) [88].

Role of combined carbon beams and nanoparticles

Porcel et al. demonstrated the radiosensitizing effect of gadolinium-based nanoparticle (GdNPs) when combined with carbon ions (150 MeV amu−1, 2.23 keV μm−1) and helium ions (150 MeV amu−1, 2.23 keV μm−1). A higher synergy was reported with carbon ions (≈19%) compared to helium ions (≈11%) [89]. Martinez et al., in their preliminary in-vitro studies, showed an enhanced production of reactive oxygen species (ROS) and DNA damage response in Glioblatoma cells lines (F98 cells lines) exposed to NP and then treated with charged particle therapy (proton, helium, carbon and oxygen).

Conclusion

Although the addition of temozolomide to radiotherapy has improved overall survival in glioblastoma over the past decade, the prognosis remains overall poor. Overcoming mechanisms of resistance, such as EGFR amplification, angiogenesis, and DNA repair system, may be beneficial. Use of new generation immunotherapy, nanoparticles and particle beam therapy seems to be also promising.

Authors' contributions

Conceptualization: Y.B.; methodology and original manuscript: Y.B.; writing draft preparation: K.D., G.L., N.H.T., HM, YB; writing-review and editing: KD, GL, NHT, MAC, CB, HR, NG, HM, YB; supervision: YB.. K.D. and G.L. have contributed equally to the manuscript.

All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Funding

None declared.

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