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REVIEW

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Radioimmunotherapy (RIT) in Brain Tumors

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Abstract

Annually, the incidence of brain tumors has slightly increased and also the patient prognosis is still disappointing, especially for high-grade neoplasms. So, researchers seek methods to improve therapeutic index as a critical aim of treatment. One of these new challenging methods is radioimmunotherapy (RIT) that involves recruiting a coupling of radionuclide component with monoclonal antibody (mAb) which are targeted against cell surface tumor–related antigens or antigens of cells within the tumor microenvironment. In the context of cancer care, precision medicine is exemplified by RIT; precision medicine can offer a tailored treatment to meet the needs for treatment of brain tumors. This review aims to discuss the molecular targets used in radioimmunotherapy of brain tumors, available and future radioimmunopharmaceutics, clinical trials of radioimmunotherapy in brain neoplasms, and eventually, conclusion and future perspective of application of radioimmunotherapy in neurooncology cancer care.

Keywords Radioimmunotherapy (RIT) · Brain tumors · Monoclonal antibody (mAb)

Introduction

Malignant brain neoplasms are generally classified as primary neoplasms, originating from the brain parenchyma itself, and metastatic tumors, raised from the sites other than the brain. Primary brain tumors are usually categorized according to the WHO classification (2016) into gliomas and meningioma as the most common tumors, respectively, and other neoplasms with fewer frequencies [1]. The most frequent original sites of the metastatic brain tumor include the lung, breast, and skin (melanoma).

Although the incidence of these tumors has slightly increased, patient prognosis is still disappointing, especially for high-grade neoplasms [2, 3]. The standard of care for brain tumors treatment consists of debulking surgery, radiotherapy, and chemotherapy in routine clinical practice. However, patients demonstrate different responses to the treatment and finally culminate in poor prognosis and death despite applying the state-of-the-art of medical care. The variable response may be partially due to intertumoral and intratumoral heterogeneity which enable tumor cells to resist against across-the-board treatment for all tumors. Beside, infiltrative characteristics of brain tumors contribute to tumor recurrence at or close to the site of a primary tumor after each surgery so that complete resection of the tumor would be impossible [4].

Therefore, an across-the-board treatment is not fit to these complex and heterogeneous neoplasms of the brain. The requirements for dealing with these tumors include providing tailored management by giving the specific drug to the specific patient based on molecular and genetic properties, where precision medicine can play a role. Precision medicine can offer a tailored treatment to meet the needs for treatment of brain tumors.

In the context of cancer care, precision medicine is exemplified by radioimmunotherapy (RIT). This method involves recruiting a coupling of radionuclide component and a monoclonal antibody (mAb) which are targeted against cell surface tumor–related antigens or antigens of cells within the tumor microenvironment [5]. This review aims to discuss the molecular targets used in radioimmunotherapy of brain tumors,

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available and future radioimmunopharmaceutics, clinical trials of radioimmunotherapy in brain neoplasms, and eventually, conclusion and future perspective of application of radioimmunotherapy in neurooncology cancer care.

Radioimmunotherapy Targets in Glioma Tumors

Tenascin-C

Tenascin-C (TN-C) is a hexabrachion polymorphic glycoprotein of the extracellular matrix (ECM) which is expressed in physiological and pathological conditions. It is expressed far and wide in pathological processes including wound healing, inflammation, and neoplasm pathogenesis as well as transient physiological expression during embryogenesis and organogenesis [6]. In the context of tumor pathogenesis, its crucial function is to facilitate the migration of tumor cells through ECM to other parts of the body [7].

Almost 90% of glioma tumors show widespread expression of TN-C, glioblastomas per se, contrary to the healthy tissues which express it only to a minor extent [6, 8]. In 2000, TN-C was found to have immunoreactivity in the tumor vessels and tumor networks of high-grade astrocytomas [9]. Moreover, TN-C deposition in the tumor vessels was higher in high-grade compared with low-grade astrocytomas [9]. Furthermore, TN-C expression correlated with proliferative indices, angiogenesis, and progressive growth pattern [9]. Regarding the key role of TN-C in the angiogenesis, proliferation, migration, and progression of the glioma tumors and the overexpression of TN-C in them, it seems that targeting TN-C would be promising as a biological target in the RIT of glioma tumors [10–16]. So far, several antibodies have been developed against TN-C which are divided into murine monoclonal antibodies (mAbs) and chimeric antibodies (cAbs). Murine mAbs against TN-C consist of BC-2, BC-4, 81C6, ST2146, ST2485, F16, and P12; and cAbs include ch81C6 [11–14, 17, 18]. These antibodies have been investigated under preclinical trials, and if they turn out to be promising, they would be translated to clinical trials [19, 16].

Epidermal Growth Factor Receptor

Epidermal growth factor receptor (EGFR) is a transmembrane protein which works as a receptor for protein ligands belonging to the epidermal growth factor family [20]. Binding of the specific ligand to the EGFR would lead to the phosphorylation of receptor tyrosine kinase and then activate subsequent signal transduction pathways which are involved in regulation of cellular proliferation, differentiation, and survival [20]. Moreover, EGFR overexpression is associated with some cancers including brain neoplasms [21]. It has been detected in about 57% of glioblastoma multiforme (GBM) tumors [21]. EGFR has a prominent role in the proliferation and survival of the tumor cells, and blocking of EGFR interrupts intracellular signal transduction. Hence, it has gained significant attraction as a biological target for RIT of brain tumors.

Thus far, two types of drug have been produced to interfere with EGFR activity which consist of mAbs against EGFR and tyrosine kinase inhibitors (TKIs) that interfere with EGFR activation. These monoclonal antibodies include nimotuzumab, cetuximab, and monoclonal antibody-425 and the TKIs comprise erlotinib and gefitinib. Both of these drug types have been investigated in preclinical and clinical trials [22–31].

Neural Cell Adhesion Molecule

Neural cell adhesion molecules (NCAMs) are cell surface glycoproteins which comprise Ig-like and fibronectin type III (FnIII) domains in their structure and belong to the immunoglobulin (Ig) superfamily. In the central nervous system (CNS), these molecules are involved in cell group formation, NCAM-mediated neurite outgrowth, and synaptic plasticity [32, 33]. Since NCAMs have been detected in several cancers ubiquitously, including brain tumors, NCAM-based target therapy of these tumors has attracted considerable attention.

Several monoclonal antibodies have been produced against NCAM comprised of ^{131}I-UJ13A, ^{131}I-ERIC-1, ^{90}Y-ERIC1, and have been tested in RIT of brain tumors through preclinical and clinical investigations [34–37].

Glioma Chloride Channels

Back in 1996, Ullrich et al. identified a chloride ion channel which is ubiquitously expressed by glioma tumor cells and intriguingly is lacking in the healthy brain tissue [38]. Furthermore, glioma chloride channel (GCC) expression is associated with tumor grade so that more than 90% of high-grade glioma tumor and all of GBM tumors express GCC [38]. Hence, GCC can be used as both a diagnostic marker and a therapeutic target.

Chlorotoxin (CTX) is a 36-amino acid peptide isolated from the giant yellow Israeli scorpion venom (*Leiurus quinquestriatus*) which successfully inhibits currents through GCC with about 80% block at 600 nM CTX [38]. TM-601 is a synthetic form of CTX that is lyophilized, sterile, and pyrogen-free compound. ^{131}I-TM-601 consists of a coupling of TM-601 as targeting agent with ^{131}I as radionuclide therapeutics [39]. This radioconjugate has passed phase I of clinical trial and the results are suggesting that phase II is indicated.

Histone H1

Tumor necrosis therapy is a novel cancer treatment approach which involves using mAbs or fragments of such to aim at the intracellular antigens belonging to the necrotic areas of tumor [40]. Tumor tissues contain areas of necrotic cells which have pathologically enhanced cell membrane permeability; therefore, the selective passage of immunoglobulins into the cells is possible [40]. Histone H1 is a linker histone which is located in the nucleus and interacts with the nucleosomal arrays for more packaging the nucleosomes into a higher-level chromatin structure [41].

This molecule is present ubiquitously in the necrotic regions of brain tumors. Hence, it could be aimed using a monoclonal antibody which is equipped with radionuclide payload [40]. ChTNT-1/B mAb is a genetically engineered chimeric mAb that specifically attaches to the DNA-bound histone H1 and forms an insoluble and non-diffusible anchor for the bound mAb [40]. Recently, it is coupled with the radionuclide ^{131}I and has been recruited in the treatment of glioblastoma tumors which is discussed later in the text [40, 42].

Neurokinin Type 1 Receptor

Neurokinin type 1 (NK-1R) is one of three kinds of mammalian tachykinin receptors family which have belonged to the 7 transmembrane G-protein coupled receptor family. NK-1R exerts its effect through the activation of phospholipase C, producing inositol triphosphate [43]. The ligand for MK-1R is substance P [44]. Regarding the overexpression of NK1-R in glioma tumors, NK-1R-targeted therapeutics for the treatment of glioma tumors have been developed. Application of ^{225}Ac-DOTA-substance P was promising in preclinical studies [45]. Late in 2018, Królicki et al. reported promising results for using ^{213}Bi-DOTA-substance P in recurrent glioblastoma [46].

Future Novel Targets

Fibulin-3

Fibulin-3 is an extracellular matrix (ECM) glycoprotein which is found in the connective tissues physiologically. Intriguingly, this molecule is lacking in the healthy brain tissue but is expressed by GBM cells and is present in the ECM of the tumor tissue [47–49]. Interestingly, fibulin-3 can activate Notch and NF-κB signaling pathways through autocrine and paracrine routes that have not been described in healthy tissues [50–52, 47]. Moreover, fibulin-3 augments the ability of invasion, vascularization, and survival in the tumor-initiating cell population of GBM tumors which is associated with poor prognosis and is considered a biomarker for the area with active progression [51, 53]. Therefore, since the fibulin-3 is a pivotal mediator in the GBM tumors and the high tumor to background ratio, it is potentially considered an appealing molecular target to kill tumor cells.

In 2018, Nandhu et al. developed a function-blocking antibody aiming fibulin-3, named mAb428.2, to kill GBM tumor cells in a mouse model [54]. The mice carrying xenograft subcutaneous or intracranial GBM received mAb428.2 via either intratumoral or intravenous (iv) injection. The results were promising, mAb428.2 could bind to the target successfully and impede the fibulin-3 to activate ADAM17, Notch, and NF-κB signaling in GBM cells and eventually slow tumor growth, invasion, and vascularization, and prolong mouse survival. Longo et al. reported anti-fibulin-3-targeted therapy of GBM can intensify anti-tumor inflammatory response [55].

Regarding evidenced studies together, fibulin-3 represents an attractive biological target to treat these tumors, especially for RIT of brain tumors where it is coupled with a radionuclide. Fibulin-3-based RIT may offer a promising therapeutics owing to a high tumor to background ratio by which it reaches tumor tissue with minimal harm to the adjacent healthy tissues. After, nearby tumor cells are in range to be destroyed through the fire effect of the radionuclide.

Routes of Drug Administration

Systemic Application of Radioconjugates

Although systemic application of the cytotoxic drugs to treat many solid tumors ensures delivery of therapeutic dose to tumor tissues, it is not the same for brain tumors. Systemic drug delivery to the brain tumors has faced several challenges of which the most significant obstacle is the intact blood–brain barrier (BBB) owing to barricading the penetration of the drugs into the brain parenchyma.

However, systemic administration of radiolabeled monoclonal antibodies for RIT of brain tumors in principle is possible. For instance, Emrich et al. achieved a positive therapeutic response following the intravenous (iv) administration of ^{125}I-labeled EGFR-mAb 425 in the treatment of patients who suffered from high-grade glioma tumors [56]. Zalutsky et al. who compared the radioconjugate uptake in the tumors depicted that, following i.v. injection of radioconjugates, the levels of ^{131}I-labeled 81C6 (tumor-specific mAbs) were fivefold higher than those of co-injected ^{125}I-labeled 45.6 (tumor-non-specific mAbs) as control radioconjugate in tissue biopsies obtained posttherapeutically. Moreover, they found that the level of ^{131}I-labeled 81C6 was up to 200 times higher than that in healthy brain tissue according to the biopsies [57].

Interestingly, Zalutsky et al. investigated dose delivery of the monoclonal antibodies to the glioma tumor tissues following intravenous and intracarotid injection of the radiolabeled mAb. They concluded that there is no advantage of drug

delivery between intravenous and intracarotid administration of the radiolabeled mAb, but the latter may be associated with carotid cannulation-related complications.

Locoregional Application of Radioconjugates

Locoregional administration of the drug is determined as direct injection of the radiolabeled monoclonal antibody either into the tumor tissue or into the tumor cyst, or a surgically created resection cavity (SCRC). This method was the standard of choice for drug delivery to the glioma tumors, mostly because it bypasses the BBB as the most challenging physical barricade against drug penetration to the brain parenchyma. Other advantages of locoregional administration are high radiation dose to the tumor with minimal systemic toxicity profile and lacking considerable interference with potential human antibodies against mouse antigen (HAMA).

Locoregional application of the drugs is performed either with convection-enhanced delivery (CED), or Ommaya reservoir. The CED method includes inserting catheters through which therapeutic design can be administered using constant, low-positive pressure bulk flow. Preclinical and clinical studies have showed that CED can offer efficient delivery of therapeutics to considerable volumes of the brain and brain tumor. However, catheter technology shortcomings and difficulties in the imaging of delivery have impeded the technique from being reliable and reproducible. Furthermore, the only completed phase III study in GBM did not demonstrate a survival advantage for the patients treated with a trial therapeutic reached via CED. Improving the development of CED is ongoing, through innovative catheter designs and imaging approaches that may improve CED to become a much more effective therapeutic delivery technique [58].

Ommaya reservoir is surgically inserted through tumor resection or during a stereotactic process. The reservoir includes a small elastic silicon reservoir, which is inserted subcutaneously and a linked catheter located in the tumor cyst or the resection cavity. All therapeutics can be administered through the reservoir straightly into the resection cavity.

Clinical Studies and Discussion

Clinical data of some selected clinical trials have been summarized in Table 1. The most commonly used monoclonal antibody for the treatment of glioma tumors is bevacizumab which is a monoclonal antibody against vascular endothelial growth factor (VEGF) [59]. Bevacizumab was thought to be the most promising agent than other agents owing to an association with a higher response rate (28–42%) and 6-month PFS (progression-free survival) (16–43%) [60]. However, although it was associated with improved quality of life and radiological pseudonormalization of tumor vasculature, it lacks overall survival benefits (median overall survival of 8–9 months) [60, 59, 61–65].

Other molecules which are aimed by radioconjugates to treat glioma tumors include tenascin-C, EGFR, NCAM, GCC, DNA-bound histone H1, and NK-1R (Table 1). The older age and lower Karnofsky performance score are associated with poorer prognosis [66]. So far, clinical investigations resulted in variable responses of the same tumor entity to the same treatment which may partly be due to intertumoral and intratumoral heterogeneity, inhomogeneous patient population, and/or presence of resistance mechanisms. The resistance mechanisms are discussed subsequently.

Resistance to Radioimmunotherapy

Although the mechanisms underlying resistance to the radioconjugates are poorly understood yet, they possibly include the inability to pass through the BBB and/or resistance to the cytotoxic effect of the radiation. Many investigations report contradicting or low therapeutic responses among patients treated with a wide variety of radioimmunotherapeutics. It is suggested that these drugs can cross the BBB sufficiently and deliver a therapeutic dose intracranially. Therefore, they destroy tumor cells through interfering with their principal biological activities.

However, subsequent recurrence could occur as the result of a reduction of pharmaceutical penetration into the BBB as the contrast-enhancing volume of tumor is diminished in the responding patients. Other rationales may include few tiny parts of the tumor that may be covered by BBB making them inaccessible, development of compensatory signaling pathways that make target inhibition useless, or extension of a primary resistant colony of tumor cells that eventually result in tumor relapse.

The intact BBB represents a physical barrier against radioconjugates to egress from the bloodstream into the brain parenchyma principally due to their large size, especially in tumor regions without contrast enhancement on conventional MR imaging. Gan et al. [67] showed that the radiolabeled ABT806i could efficiently penetrate into tissues of EGFR-expressing tumors with BBB disruption. This observation is suggesting the fact that deep penetration of the radioconjugates into tumor tissues is possible where BBB is disrupted, as it usually occurs in high-grade gliomas.

Expression of the target antigen is an essential requirement for effective therapy with antibody-based therapeutics. A different response to the same treatment in patients with one tumor entity indicates that intratumoral and intertumoral heterogeneity contribute to the variable expression of the target antigen and result in the development of drug resistance. For instance, no therapeutic response to ABT-414 has been achieved when the prerequisite target antigen EGFRvIII was

Table 1 Preclinical and clinical radioimmunotherapy trials in brain tumors

Selected clinical trials

Drug	Design	Phase of study	Results	Toxicities	Comments
Radioimmunotherapy in newly diagnosed neoplasms					
^{125}I-mab425[66]	Intravenous of intra-arterial administration of radiolabeled anti-EGFR mAb	I\II	Despite acute toxicities (nausea, vomiting) in one patient who received > 60 mCi ^{125}I-mAb425, 50 mCi of drug was well tolerated	Single arm: GBM patient ORS: 4–150 months AA patient ORS: 4–270 months	GBM and AA patients younger than 40 years old and Karnofsky performance score > 70 showed a median survival of 22.5 and 65 months, respectively
^{125}I-mAb 425 [67]	Intravenous administration of radiolabeled mouse anti-EGFR antibody (with radiotherapy ± temozolomide)	II	Occasional nausea, flushing, hypotension, skin irritation, HAMA (only in 4 of 192 patients)	ORR: NA mOS: 20.4 months 6-month PFS: NA	Median OS was 10.2 months for a cohort of patients receiving radiotherapy alone
^{131}I-81C6 [68]	Locoregional delivery of radiolabeled mouse anti-tenascin antibody (with radiotherapy + chemotherapy)	Pilot study	Seizures (including *status epilepticus*), hematological, neurological, infective, thrombotic complications	ORR: NA mOS: 22.6 months 6-month PFS: NA	NA
^{131}I-BC2/BC4 [19]	Locoregional delivery of radiolabeled mouse anti-tenascin antibody (with conventional surgery and post-operative radiotherapy ± chemotherapy)	I/II	Headaches, HAMA	ORR: NA* mOS: 19 months 6-month PFS: NA	Data shown are only for patients with glioblastoma mOS: 25 months for patients with small-volume (< 2 cm^3) disease
Radioimmunotherapy in recurrent disease					
^{188}Re-nimotuzumab [69]	Radiolabeled anti-EGFR mAb administered via Ommaya reservoir	I	Neurological deterioration, radionecrosis, liver function test abnormalities	ORR: NA mOS: 19 months 6-month PFS: NA	MTD was 3 mg for 10 mCi ^{188}Re-labelled antibody
^{211}At-ch81C6 [70]	Radiolabeled chimeric anti-tenascin mAb administered via Rickham reservoir	I	Seizures, headaches, aphasia, numbness, visual deficit, nausea, fatigue, infections, HAMA	ORR: NA* mOS: 14.3 months 6-month PFS: NA	Data shown are only for patients with glioblastoma
^{131}I-BC2/BC-4 [19]	Radiolabeled anti-tenascin mAb	I/II	Headaches, HAMA	ORR: 22% mOS: 21 months 6-month PFS: NA	Data shown are only for patients with glioblastoma
Cotara (^{131}I-chTNT-1/B) [42]	Radiolabeled anti-histone H1 antibody delivered via CED	II	Headaches, hemiparesis, seizures, cerebral edema, confusion, agitation, memory impairment, reduced consciousness, fatigue, abdominal pain, catheter complications	ORR: 18% mOS: 9.5 months 6-month PFS: NA	Efficacy data shown are only for patients with recurrent disease receiving 1.25 mCi/cm^3 and 2.5 mCi/cm^3
^{131}-I-TM-601 [39]	Radiolabeled TM-601 against GCC locoregionally delivered via Rickham reservoir	I	Transient mild to moderate adverse events, and sporadic serious events including generalized seizure, confusion, pneumonia, ventricular dilation, cerebral hematoma, headache, dysarthria	Single-arm study ORR: NA mOS: 27 months 6-month PFS: NA	Patients were divided into three groups. The group that received 0.50-mg dose has mOS of 77.6 months
^{213}Bi-DOTA-substance P[46]	Radiolabeled DOTA-substance P against NK-1R	Pilot	Face flushing, epileptic seizure, transient worsening of paresis	Single-arm study ORR: NA mOS: 23.6 months 6-month PFS: 2.7 months	All of the patients who developed epileptic seizure have had sporicidal seizure before the treatment

CED, convection-enhanced delivery; *HAMA*, human anti-mouse antibody; *MTD*, maximum tolerated dose; *NA*, not available; *mOS*, median overall survival; *PFS*, progression-free survival; *ORR*, overall response rate; *NK-1R*, neurokinin type 1 receptor; *GCC*, glioma chloride channel

absent [68]. This observation and similar results may intensify the fact that assessing the expression level of target antigen is mandatory before initiating a molecular-based target therapy, particularly in heterogeneous tumors.

Acquired resistance to the cytotoxic payload is another way in which the tumor cells shield against therapeutics. In other cancer types (for instance, prostate cancer), tumors with an almost similar expression level of target antigen may show various therapeutic responses to the same treatment [69]. The same results were achieved from a preliminary study of resistance mechanisms to ABT-414 in patients with glioblastoma [70].

Regarding the large body of evidence, it is necessary to note that although the mechanisms of resistance to the radioconjugates are poorly understood yet, they constitute a major cause of failure in treatment of high-grade gliomas. Indeed, a better understanding of molecular characteristics and interaction of glioma tumors would give us more insight into determination of resistance mechanism pathways and detection of a more specific target for the treatment.

Future Prospective

According to a large body of evidence, radioimmunotherapy represents a promising method in the treatment of brain tumors. Radioimmunotherapy provides targeted delivery of potent radionuclide payloads as a distinctive mechanism of action by which a large amount of radionuclide is delivered to the tumor tissues with a minimum of systemic toxicity. This potential is exemplified using radiolabeled anti-EGFR in patients suffering from glioblastoma where the patient population who are treated with many anti-EGFR agents (such as TKIs or naked antibodies) have failed to demonstrate therapeutic efficacy, but radiolabeled anti-EGFR therapeutics was promising.

Regarding the heterogeneous genetic and molecular properties of high-grade gliomas, GBM per se, the combination of a radionuclide with the antibodies with intrinsic anti-cancer properties, is a preferred choice through the development of RIT therapeutics. Another eminent designated antibody characteristic is tumor specificity of the target along with copious and/or ubiquitous expression of the target antigen. Essential features of a successful radiolabeled antibody include sufficient binding capacity to the target, uniform distribution of the drug within the tumor tissue, and lack of binding to healthy tissues.

As a result of the high specificity of RIT therapeutics, both inadequate expression of targeted-antigen and resistance to the radioconjugates, either antibody or radionuclide, would lead to treatment failure typically. To achieve an ideal radiolabeled antibody, including specified tumor targeting without systemic toxicities, it is necessary to launch customized preclinical and clinical trials. Foremost of all, improvements in the capacity to precisely quantify antigen expression in tumor tissue noninvasively should be prioritized. Accurate targeted-antigen quantification can serve as a patient selection strategy at diagnosis, a modality for resistance detection or guidance in the treatment selection at the progression of disease.

The proofs of preclinical studies indicate that dual-targeted treatment strategies can result in more successful outcomes in comparison with each separate targeted approach. The dual-targeting therapy approach involves using a combination of targeted therapeutics that aim at two different populations of tumor cells simultaneously. Interestingly, newly produced bispecific antibodies are the other types of this approach [71–74].

However, all the new potential combinatorial approaches would necessitate robust phase I investigations to ascertain that the toxicity profile is acceptable and to determine combination-dosing schedules for future studies.

Compliance with Ethical Standards

Conflict of Interest Ali Gholamrezanezhad, Hossein Shooli, Narges Jokar, Reza Nemati, and Majid Assadi declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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