ELSEVIER

Critical Reviews in Oncology/Hematology 80 (2011) 54–68

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

A comprehensive outlook on intracerebral therapy of malignant gliomas

Carlo Buonerba[a,1], Giuseppe Di Lorenzo[a,b,*,1], Alfredo Marinelli[a,b], Piera Federico[a], Giovannella Palmieri[a,b], Martina Imbimbo[a], Pio Conti[c], Gianfranco Peluso[d], Sabino De Placido[a], John H. Sampson[e]

[a] *Cattedra di Oncologia Medica, Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Università degli Studi Federico II, Naples, Italy*
[b] *Centro di Riferimento Tumori Rari (CRTR) - Regione Campania, Italy*
[c] *Immunology Division, Department of Oncology and Neuroscience, University of Chieti, Italy*
[d] *Institute of Protein Biochemistry, CNR, Naples, Italy*
[e] *Division of Neurosurgery, Department of Surgery Duke University Medical Center, Durham, NC, United States*

Accepted 1 September 2010

Contents

1. Introduction 55
2. Intracerebral delivery techniques 55
   2.1. Manual injection and implantable reservoirs 55
   2.2. Biodegradable drug carriers 58
   2.3. Convection-enhanced delivery 58
3. Conventional chemotherapy agents 60
   3.1. Gliadel® 60
   3.2. Polymer-based delivery of agents other than carmustine 60
   3.3. Mitoxantrone and other chemotherapics 63
4. Radioactive agents 63
   4.1. Anti-tenascin antibodies 63
   4.2. COTARA and others 64
5. Receptor targeted toxins 64
   5.1. IL-13 and EGF receptors 64
   5.2. Transferrin and IL-4 receptors 65
6. Concluding remarks 65
   Search criteria 66
   Contributors 66
   Conflict of interest 66
   Funding 66
   Reviewers 66
   Acknowledgements 66
   References 66
   Biography 68

Abstract

Glioblastoma multiforme (GBM) is the most frequent and aggressive malignant glioma (MG), with a median survival time of 12–15 months, despite current best treatment based on surgery, radiotherapy and systemic chemotherapy. Many potentially active therapeutic agents are not effective by systemic administration, because they are unable to cross the blood–brain barrier (BBB). As intracerebral administration bypasses the BBB, it increases the number of drugs that can be successfully delivered to the brain, with the possibility of minor systemic

* Corresponding author. Tel.: +39 081 7462053.
E-mail address: giuseppedilorenzoncol@hotmail.com (G. Di Lorenzo).
[1] Equally contributed.

1040-8428/$ – see front matter
doi:10.1016/j.critrevonc.2010.09.001

toxicity and better effectiveness. This review summarizes the results of the extensive clinical research conducted on intracerebral therapy. Biodegradable drug carriers, implantable subcutaneous reservoirs and convection-enhanced delivery (CED) represent the main techniques for intracerebral delivery, while conventional chemotherapy agents, radiolabeled antibodies and receptor-targeted toxins are the main classes of drugs for intracerebral therapy. At the present time, biodegradable carmustine wafers, commercialized as Gliadel®, are the only FDA-approved treatment for intracerebral chemotherapy of MG, but intracavitary delivery of mitoxantrone and radiolabeled antitenascin antibodies via implantable reservoirs has yielded promising results in uncontrolled trials. The pressure-driven flow generated by CED can potentially distribute convected drugs over large volumes of the brain, independently on their intrinsic diffusivity. Nevertheless, prominent technical problems, like backflow, are yet to be properly addressed and contributed to the disappointing results of two phase III trials that investigated CED of cintredekin besudotox and TransMid™ in patients with recurrent GBM.

Keywords: Brain neoplasm; Convection enhanced delivery; Drug delivery system; iPlan Flow

1. Introduction

Among malignant gliomas (MGs), which also include anaplastic astrocytoma (AA), oligodendoglioma (AO) and oligoastrocytoma (AOA) [1], glioblastoma multiforme (GBM) is the most frequently occurring and deadliest with a median survival from diagnosis of 12 to 15 months [2]. Due to its infiltrative nature, current best treatment, consisting of combination of surgery and radiotherapy with concomitant and adjuvant systemic temozolomide(TMZ) [2], almost universally fails to eradicate the tumor, which recurs within 2 cm of the original lesion in about 90% of cases [3]. These treatment modalities can be used for relapsing disease but factors like local and systemic cumulative toxicity, necessity of sparing brain parenchyma and intervening clinical deterioration limit their effectiveness in prolonging survival, which remains in the dismal range of 6–8 months after recurrence [4].

The constant pattern of loco-regional but not extra-cerebral relapse of MGs, along with an expected improvement in the pharmacokinetic and toxicity profile of the administered agents, which translates into a reduced amount of drug dispersed throughout body, is among the reasons that make intracranial delivery conceptually sound. One major attractiveness of such an approach lies in its potential to bypass the blood–brain barrier (BBB), thus enormously expanding the armamentarium of drugs that can be effectively delivered to the brain. In fact, although the BBB may be disrupted in the necrotic core, its preservation in tumor periphery, as well as in small tumor foci throughout the brain parenchyma, prevents therapeutics with a high molecular weight or an ionic charge from being successfully delivered in such areas by systemic administration [5]. While intraventricular injection might be considered in the rare cases of neoplastic meningitis caused by MGs [6], its use to treat parenchymal lesions suffers from prohibitive diffusion limitations, depending on the blood–CSF barrier [7]. On the other hand, the novel convection-enhanced delivery (CED) [8] technique, biodegradable drug delivery carriers [10], subcutaneous reservoirs [11] and even simple manual injection [5] can successfully circumvent the BBB and allow interstitial administration both in tumor and brain tissues. CED is particularly intriguing because it provides a pressure-driven flow that overcomes the boundaries imposed by the diffusion process on molecular size, shape and charge. While CED has only been employed in phase III trials in the past few years [9], controlled-release 3.9% carmustine wafers have already been commercially available as Gliadel® since the late 1990s and represent the gold standard in the field of intracerebral therapy (Fig. 1) [10].

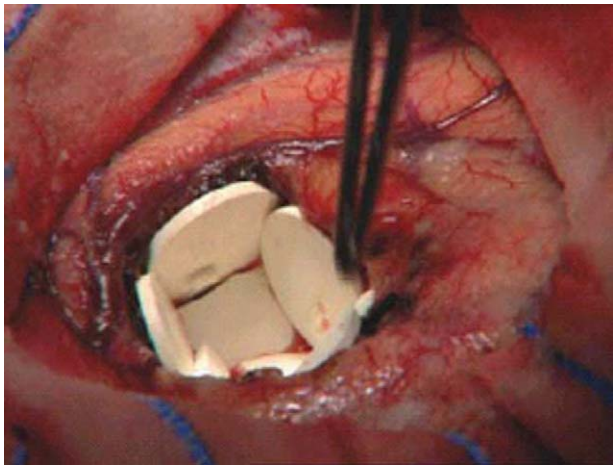

Fig. 1. Intracerebral implantation of Gliadel. Up to 8 wafers can be placed in the resection cavity after tumor excision.
Reprinted by permission from Macmillan Publishers Ltd: Lesniak MS, Brem H. Targeted therapy for brain tumours. Nat Rev Drug Discov. 2004;3(June (6)):499–508. Copyright (2004).

The aim of this review is to summarize the results of the extensive clinical research on intracerebral therapy, which is interestingly heterogeneous as far as tested agents and employed techniques are concerned. Clinical trials on conventional chemotherapy agents, radioactive agents and receptor targeted toxins will be presented along with a detailed description of the techniques used for intracerebral delivery.

2. Intracerebral delivery techniques

2.1. Manual injection and implantable reservoirs

Simple manual injection into brain or tumor tissues was widely used in the past [5], but it has been little employed

Table 1
Delivery by subcutaneous reservoirs or manual injection in patients with malignant brain tumors.

Investigated agent for local delivery	Author Publication year	Trial Main inclusion criterion	GBM/recruited patients	Study treatment Local delivery site Local delivery technique	Schedule	Principle toxicity related to local treatment	Response PFS	Survival after treatment
Mitoxantrone	Boiardi [43] 2004	Retrospective trial Resectable Recurrent GBM	276/276	A: 161p, sTMZ B: 50p, surgery + sTMZ C: surgery + sTMZ + local treatment SCRC Ommaya reservoir	sTMZ: 200 mg/m^2 d1–5, q28 lMTX: 4 mg d1 and 5, q28	Reservoir-related infection	A, PFS6: 39.3% B, PFS6: 64% C, PFS6: 70.7%	A: 5 mo (4–6) B: 8 mo (6–10) C: 11 mo (9–13)
Mitoxantrone RIT Caelyx®	Boiardi [45] 2003	Pilot trial Resectable Recurrent GBM	58/58	Surgery + sTMZ in all patients + A: 20p, MTX B: 26p, lMTX + lRIT C: 12p, lCaelyx SCRC Ommaya reservoir	TMZ: 200 mg/m^2 d1–5, q30 A MTX: 4 mg d1 and 5, q30 B MTX: 4 mg d1, q20 ^{90}Y-BC-4: 5–25 mCi every 10 w C Caelyx:d1, 5, 10, 15, 20 q 40	Reservoir-related infection	A, PFS6: 55% B, PFS6: 61% C, PFS6: 50%	A: 11 mo B: 13 mo C: 13 mo
Doxorubicin	Voulgaris [44] 2007	Pilot trial Resectable Recurrent MG	9/10	Tumor Ommaya reservoir	0.5 mg d1–10	Bifrontal headache	5/10 radiologic response	9.3 mo, 39.9 w (8–73)
Bleomycin	Patchell [12] 2002	Phase I Resectable Recurrent MG	9/9	Surgery + local treatment Tumor or SCRC Modified Ommaya reservoir	5–34 U every week	Headache, skin ulcers	MTD: 16 U/w PFS: 17 w (3–48)	6 mo (2–22)
^{131}I-m81C6	Reardon [47] 2002	Phase II Resectable Newly diagnosed MG	27/33	Surgery + local treatment SCRC Rickham reservoir	120 mCi at surgery	Irreversible neurologic toxicity	Not reported	GBM: 18.5 mo, 79.4 w (95% CI: 61.4–∞)
^{131}I-m81C6	Reardon [48] 2006	Phase II Resectable Recurrent MG	33/43	Surgery + local treatment SCRC Rickham reservoir	100 mCi at surgery	Reversible neurologic toxicity	Not reported	GBM: 14.9 mo, 63.9 w (95% CI: 38.8–90.0)
^{131}I-m81C6	Reardon [49] 2008	Phase II Resectable Newly diagnosed MG	15/21	Surgery + local treatment SCRC Rickham reservoir	25–150 mCi to deliver 44 Gy boost	Reversible neurologic toxicity	Not reported	GBM: 21.1 mo, 90.6 w (95% CI: 73.3–97.1)

^{131}I-ch81C6	Reardon [50] 2006	Phase I Resectable MG	38/47	Surgery + local treatment SCRC Rickham reservoir	80–120 mCi at surgery	Hematologic toxicity	Not reported	Newly diagnosed GBM: 20 mo, 86.1 w (95% CI: 70.1–99.1) recurrent GBM: 11.4 mo, 48.9 w (95% CI: 30.4–83.3)
^{211}At-ch81C6	Zalutsky [51] 2008	Phase I Resectable Recurrent MG	4/18	Surgery + local treatment SCRC Rickham reservoir	1.9–9.3 mCi at surgery	Reversible neurologic toxicity	MTD: not identified	GBM: 12.1 mo, 52 w (95% CI: 33–76 w)
^{131}I-M2–4	Riva [52] 2000	Phase II Resectable MG	74/91	Surgery + local treatment SCRC Rickham/Ommaya reservoir	45 mCi repeated every 30–90 days	None reported	Response rate GBM: 57.6%	GBM: 19 mo
^{90}Y-M2–4			35/43		20 mCi repeated every 30–90 days		Response rate GBM: 66.6%	GBM: 20 mo
MTX + ^{90}Y-M2–4	Boiardi [53] 2000	Phase II Operable Recurrent MG	26/26	Surgery + sPCV in all patients + A: 20p, lMTX + lRIT B: 6p, lRIT SCRC Ommaya reservoir	sPCV: every 6 w lMTX: 4 mg d1, q20 l^{90}Y-BC-4: 5–25 mCi every 10 w	Reservoir-related infection	A, PFS: 8 mo B, PFS: 8 mo	A: 13 mo B: 12 mo
^{90}Y-DOTAGA-SP ^{177}Lut-DOTAGA-SP ^{213}Bi-DOTAGA-SP	Kneifel [55]	Pilot trial WHO 2–4 Gliomas	14/20	Surgery + local treatment SCRC or Tumor Subcutaneous reservoir	10.1–202 mCi ^{90}Y-DOTAGA-SP: 15p ^{177}Lut-DOTAGA-SP: 3p ^{213}Bi-DOTAGA-SP: 2p	Perifocal edema	Neurologic improvement 5/14 GBM	11 mo (range, 6–24 mo)
^{188}Re-nimotuzumab	Torres [56] 2008	Phase I Recurrent MG	8/9	Surgery + local treatment SCRC Ommaya/Richkam reservoir	10–15 mCi	Neurologic toxicity	Not reported	Not reported

mo = months, w = weeks, d = days, l = local, s = systemic, MG = malignant gliomas, GBM = glioblastoma multiforme, MTD = maximum tolerated dose, CI = confidence interval, PFS = progression free survival, RT = radiotherapy, TMZ = temozolomide, MTX = mitoxantrone and SCRC = surgically created resection cavity.

since less invasive and more effective techniques have become available in the last two decades.

The Ommaya reservoir has been extensively used for intracavitary delivery. It is composed of a mushroom-shaped reservoir, which is implanted subcutaneously, connected to an outlet catheter, which is positioned within the tumor bed through a burr hole in the skull [11]. Therapeutic agents are first injected transcutaneously in the reservoir, and then delivered through the catheter by manual compression [5]. The Rickham is similar to the Ommaya reservoir. Its smaller size diminishes the risk of infection, but also makes it more difficult to locate the reservoir under the skin [11]. In order to obtain a continuous rather than bolus delivery, the Ommaya reservoir has been modified by adding a polyvinyl alcohol semipermeable membrane between the reservoir and the delivery tube [12]. Table 1 shows reviewed trials employing implantable reservoirs for intracerebral delivery.

Motor pumps, like Medtronic Synchromed Drug Administration System (DAS), are also subcutaneously implanted and percutaneously refillable, but unlike the Ommaya reservoir, they can provide a prolonged and controlled intracerebral delivery [5]. They have found little application in the field of intracerebral delivery for MGs, because of their low flow rate and limited capacity.

2.2. Biodegradable drug carriers

Biodegradable drug delivery carriers can be easily implanted, with no additional burden for patients undergoing surgical tumor excision, and they do not need reintervention to be removed, as they are metabolically degraded and eliminated. A wide variety of chemical compounds have showed potential use as biodegradable drug delivery carriers. Among these, polyanhydride polymers display favorable features in terms of biocompatibility and degradation process. In fact, the non-enzymatically mediated erosion that occurs on the surface, but not inside of the polymer molecule, provides a controlled drug release rate and a predictable, host-independent pharmacokinetic profile [13]. Clinically, the most widely used polyanhydride for intracerebral drug delivery is a biocompatible [14] copolymer of the two monomers bis(p-carboxyphenoxy)propane (PCPP) and sebacic acid (SA). PCPP and SA are employed in a 20:80 molar ratio in Gliadel®. Interestingly, such a ratio can be modified to shape the kinetics of carmustine delivery [15]. Although the number of chemotherapeutics employed in preclinical studies for polymer-mediated intracerebral delivery is large [16], the association of PCPP-SA and carmustine is one of the few to have been used in humans. Preclinical animal studies [17,18] assessed Gliadel to have an excellent safety profile, also in combination with radiotherapy [18], and indicated that carmustine release was almost complete in the rabbit brain within a week [17]. A matter of concern about Gliadel is carmustine penetration depth. In fact, in spite of carmustine's high lipophilicity, factors like drug elimination rate, brain peculiar extra cellular matrix and tumor local environment [19] might hamper its diffusion through the brain parenchyma. Taking into account preclinical data from radiolabeled carmustine studies in rats, rabbits and monkeys, as well as the results of a three-dimensional computerized model, it was concluded that the drug could not diffuse more than 1–2 cm away from the implantation site [10].

Biodegradable copolymer polylactic–coglycolic acid (PLGA) microparticles [20] can be manually injected into the brain parenchyma. Although PLGA microspheres carrying 5-fluorouracil (5-FU) showed a penetration depth of only 3 mm in the rat brain [21], multi-point injection might satisfactorily cover the whole target volume. Until the present time, PLGA particles have been used in clinical trials [20] to deliver radiosensitizing 5-FU, although the spectrum of anticancer drugs incorporable in PLGA microspheres is wide [19].

Biocompatible hemostatic agents, such as 6-carboxylcellulose [22] or Surgifoam [23], are also a feasible option and have been employed in sporadic clinical studies.

2.3. Convection-enhanced delivery

A motor-driven pumping device connected to a catheter stereotactically implanted in the brain generates a so-called 'bulk flow', which can deliver the infusate in larger cerebral volumes in comparison to diffusive flow [24]. The pressure-driven spreading of infused solutes through the interstitium does not depend on their intrinsic diffusivity and continues throughout the time CED is performed (a few days in humans), to end abruptly when the procedure terminates [25].

A certain degree of back flow along the catheter is inevitable, due to the very physics of the CED process [26]. Backflow is a major concern because it can cause the infusate to miss the target volume and drain into ventricular or subarachnoid spaces [27,28], with risk of chemical meningitis. In non-human primates and canines, MRI showed that 18.5% of CED infusions of liposomes bearing an MRI contrast agent leaked into the CSF [27]. Similarly in humans [28], SPECT (Single Photon Emission Computed Tomography) showed that only 11 out of 21 infusions of cintredekin besudotox (CB) plus ^{123}I-labeled human serum albumin (^{123}I-HSA) provided an adequate volume of distribution (Vd), because of leakage phenomena. The chances of backflow are increased by higher infusion rates and volumes [25]. As backflow is also more likely with large-sized catheters [25], Fiandaca et al. [29] constructed a step-design catheter, composed of a 27-gauge (0.2 mm) needle which featured at its tip a glued-in silica tubing presenting a smaller diameter of about 0.1 mm. Such a catheter could provide a flow rate up to 5 μl/min in a preclinical study, but the rate of ineffective delivery was still high, as already indicated [27].

The geography of the brain area where delivery occurs also affects the Vd, because white matter fibers offer a low-resistance pathway to convection, as compared to grey matter tissue [24]. A computerized model (iPlan Flow) by BrainLab AG (FeldKirchen, Germany) takes into account both

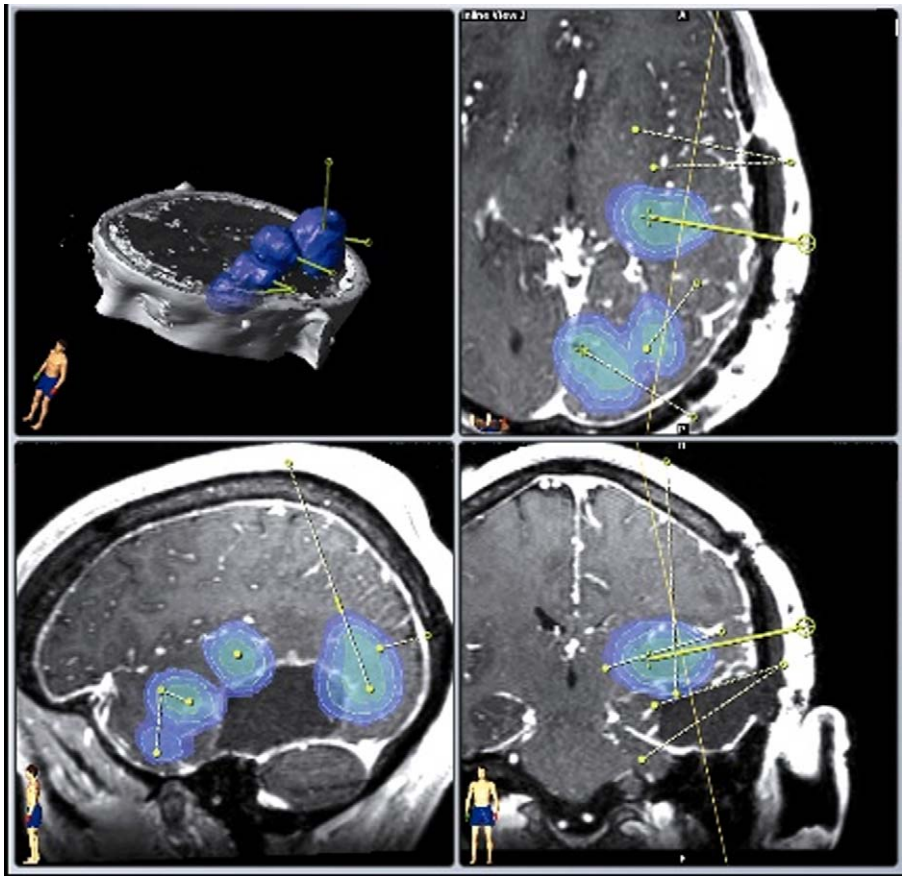

Fig. 2. Computerized simulation on MRI images of predicted CED distribution volume (blue areas) on the basis of different catheter trajectories (yellow lines). Tridimensional representation of the predicted volume of distribution is also reported.
Reproduced from Ref. [30], by permission of Oxford University Press. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

patients' brain geography and estimated backflow to simulate the Vd of CED infusions and aid to select the most appropriate catheter trajectory (Fig. 2). This FDA-approved software has been retrospectively tested in 8 patients who had perioperatively received CED of cintredekin besudotox + ^{123}I-HSA. Flow rate and MRI and DT (diffusion tensor) MRI data set were given as input. The software was firstly run to detect deep sulci, resection cavities and ependymal surfaces and then it estimated the Vd on the condition that the calculated backflow did not cause the infusate to leak into a 'sulcus'. Globally, the software was judged as 'clinically useful' in 84.6% of cases. In fact, sulcus detection algorithm identified problematically placed catheters with a sensitivity of 5/7 and a specificity of 7/7 (Fisher's exact test, $p = 0.021$), while 6 out of 8 simulated Vd matched SPECT Vd by at least 50% [30]. Recently, a retrospective analysis employing iPlan Flow has been performed on a sample of 59 recurrent GBM patients enrolled in the phase 3 PRECISE trial (Phase 3 Randomized Evaluation of Convection-Enhanced Delivery of IL13-PE38QQR Compared to Gliadel Wafer with Survival Endpoint in Glioplastoma Multiforme at First Recurrence) [9], who had received intraparenchymal CED of cintredekin besudotox in the walls of the SCRC. Three catheter positioning criteria were employed in the PRECISE trial to score catheter position from 0 to 2, according to the number of fulfilled criteria. Simulation with iPlan Flow of the coverage volume of the 1-cm and 2-cm penumbra and of the T2 edema area around the SCRC showed two important results. Firstly, a significant correlation was found between catheter positioning score and simulated coverage volume. Secondly, average simulated coverage volume was very low (17.5% of the 1-cm penumbra, for example), which may explain the disappointing results of the PRECISE trial. On the basis of this analysis, it can be concluded that fulfillment of catheter positioning criteria does have an impact on Vd, but is not sufficient to produce an adequate coverage area, which could have been in excess of 60% of the target volume, if iPlan Flow had been employed in the PRECISE trial [9].

Real time imaging of the convection process could allow identification and interruption of an ineffective delivery. Although SPECT with ^{123}I-HSA can effectively estimate the Vd, ^{123}I-HSA presents some important drawbacks as a surrogate tracer. Firstly, its limited half-life requires SPECT to be performed within 2 days after initiation of CED. Secondarily, it could overestimate the Vd of a drug targeted to specific receptors on brain cells, because it does not bind to the

receptors that the convected drug binds to [28]. Gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) is low-cost and ready available and might be advantageously employed to monitor CED especially when co-localized with the drug in a liposome [31,32,33]. In eight patients with MG receiving CED of HSV thymidine kinase (HSV-tk) gene–bearing liposomes, Gd-DTPA seemed to be a valid surrogate tracer, because it colocalized with treatment-related changes on $^{[11C]}$-L-methionine (MET) PET [33]. However, since the low molecular weight and high diffusivity of Gd-DTPA might cause it to overestimate the Vd of high molecular weight drugs [31], pre-clinical studies have used Gd-DTPA conjugated to albumin or loaded in liposomes for more accurate monitoring of intracerebral delivery [25]. Gd-DTPA itself could still successfully monitor high molecular weight drugs delivery, on the condition that its infusion rate is corrected to account for its different tissue loss and diffusivity, with respect to the co-infused drug [32].

Even without the use of a surrogate tracer, T2-weighted and diffusion weighted (DW) MRI can be of use to monitor CED. In 7 recurrent MG patients receiving cintredekin besudotox + ^{123}I-HSA, increase in signal around the catheter on T2-weighted MRI could detect if infusion was totally ineffective, but it was of little use to estimate the Vd if delivery occurred in contrast-enhanced areas [34]. In 15 recurrent GBM patients receiving paclitaxel, hyperintense signal that appeared on DW-MRI as early as 24 h after treatment initiation precipitated lytic responses later observed on T1-weighted images [35]. The small number of recruited patients is the major limitation of these two studies. Nevertheless, they provide sufficient evidence that widespread MRI imaging can monitor CED, although it cannot reliably estimate the Vd, especially without using a surrogate tracer.

Reviewed clinical trials using CED are showed in Table 2.

3. Conventional chemotherapy agents

3.1. Gliadel®

Two well designed, randomized controlled trials have compared Gliadel to placebo in recurrent [36] and newly diagnosed [37] MG. After tumor excision, 222 patients with recurrent MG were randomized to receive either Gliadel (110 patients, 72 GBM) or a placebo (112 patients, 73 GBM) in the surgically created resection cavity (SCRC). While 64% vs. 44% ($p = 0.02$) of GBM patients in the Gliadel and in the placebo group, respectively, were alive at 6 months, the difference in survival since recurrence between the two arms as a whole was not statistically significant (31 weeks vs. 23 weeks, estimated hazard ratio = 0.83, $p = 0.19$). If treatment and prognostic factors were taken into account in a multiple regression analysis, the estimated risk of death was statistically significantly lower in the Gliadel group of both the whole sample of patients (hazard ratio 0.67, $p = 0.006$) and the sample of GBM patients only (hazard ratio 0.67, $p = 0.02$). In another phase III trial, 240 patients with newly diagnosed MG were randomized to be implanted either Gliadel or a placebo in the SCRC, prior to external radiotherapy (XRT) [37]. The survival advantage for the Gliadel group (120 patients, 101 GBM) as compared to the placebo group (120 patients, 106 GBM) was statistically significant (13.9 months vs. 11.6 months, $p = 0.03$) and was maintained for the GBM subgroup, if prognostic factors were properly considered. Gliadel was reported to be safe in both trials, with hemiplegia, brain edema, confusion and seizures being the most frequent neurologic adverse events recorded in both groups, although serious intracranial infection (4 /110 vs. 1/112) [36], intracranial hypertension (9 /120 vs. 2 /120) [37] and CSF leak (6 /120 vs. 1/120) [37] were more frequent in the Gliadel group than in the placebo group, respectively. On the basis of the results of both these studies, Gliadel received FDA approval for newly diagnosed MG or recurrent GBM and currently represents the only FDA-approved agent for intracerebral chemotherapy.

Systemic therapy with O6-benzylguanine (O6-BG) and carmustine can revert the resistance conferred by O6-alkylguanine-DNA alkyltransferase to carmustine, at the cost of increased bone-marrow toxicity. A single-arm, phase II trial accruing 51 patients with recurrent GBM administered intravenous O6-BG (continuous infusion of 30 mg/m^2/day on days 1 through 5, bolus injection of 120 mg/m^2 on days 1, 3, and 5) after implantation of up to 8 Gliadel wafers. Although a remarkable median survival after treatment of 50.3 weeks was reported, the incidence of grade 3 CSF leak, brain/CSF infection and hydrocephalus was higher than expected on the basis of the phase III trials [36,37], being 19.2, 13.4 and 9.6%, respectively [38]. This trial, as well as the two large trials reported [36,37], did not investigate the impact of concomitant or sequential systemic chemotherapy. Local carmustine and systemic temozolomide might present synergistic activity, because of their different time to peak effect and because of the possibility for temozolomide to revert resistance to carmustine [39]. The feasibility of a combination of Gliadel®, XRT and systemic temozolomide has been demonstrated by a prospective phase II trial [40] in 41 newly diagnosed patients (40 GBM and one AA) and by a retrospective study [41] in 33 patients with primary GBM, which reported a median survival since diagnosis of 19.7 and 20.7 months, respectively. The safety profile reported by both studies was comparable to the one of XRT + Gliadel or XRT + temozolomide treatments.

3.2. Polymer-based delivery of agents other than carmustine

Ninety-five patients with radiological diagnosis of MG were randomized to receive intracerebral administration of 130 mg of radiosensitizing 5-FU and XRT, or XRT only. 5-FU was incorporated in 40 μm PLGA microparticles and stereotactically injected in the walls of the resection cavity up to a depth of 2 cm. Several recruited patients were excluded

Table 2
Clinical trials investigating CED in patients with malignant brain tumors.

Investigated agent	Author	Publication Year	Trial Main inclusion criterion	GBM patients/ all recruited patients	Total administered dose Total flow rate Delivery site	MTD	Principle severe treatment related toxicity	Response PFS	Overall survival
Paclitaxel	Lidar [35]	2004	Phase I/II Recurrent MG	13/15	0.6–1.2 mg/ml × 12–33 ml 5 μl/min × 2–5 d Tumor	0.5 mg/ml × 33 ml	Chemical meningitis	11/15 partial or complete responses	7.5 mo (0–14), 2 living patients excluded
	Pöpperl [46]	2005	Phase I/II Recurrent GBM	8/8	0.25–0.5 mg/ml × 36 ml 5 μl/min × 6 d Tumor	0.25 mg/ml × 36 ml	Skin necrosis	PFS: 8 mo	10 mo
	Tanner 26]	2007	Phase I/II Recurrent GBM	8/8	0.25–0.5 mg/ml × 36 ml 5–6.6 μl/min × 6 d Tumor	0.25 mg/ml × 36 ml	Skin necrosis	6/8 with MRI radiographic changes	13.5 mo (mean), 2 patients excluded
Cotara	Patel [54]	2005	Phase I Recurrent or unresectable newly diagnosed MG	45/51	20 or 40 mCi or 1–3 mCi/cm^3 CTV 4.5–18 ml 3 μl/min × 1–2 d Tumor	1.5 mCi/cm^3 CTV	Neurologic symptoms	Not reported	Not reported
			Phase II Recurrent or unresectable newly diagnosed MG		1–3 mCi/cm^3 CTV 4.5–18 ml 3 μl/min × 1–2 d Tumor			1/11 partial response 6/11 stable disease on MRI	8.8 mo, 37.9 w (95% CI: 24.1–69.4) in 12 recurrent GBM
Cintredekin besudotox	Kunwar [58]	2007	Phase I Recurrent operable MG	46/51	0.25–1.0 μg/ml × 72–108 ml 12.5 μl/min × 4–6 days Parenchyma surrounding the resection cavity	0.5 μg/ml × 108 ml	Hemiparesis	Not reported	10.7 mo, 45.9 w (95% CI: 37.4–59.3)

Table 2 (*Continued*)

Investigated agent	Author	Publication	Year	Trial Main inclusion criterion	GBM patients/ all recruited patients	Total administered dose Total flow rate Delivery site	MTD	Principle severe treatment related toxicity	Response PFS	Overall survival
	Sampson	[9]		Phase III Recurrent operable MG	294/294 196 patients: CED 98 patients: Gliadel	0.5 μg/ml 12.5 μl/min		Not reported	4.1 mo, 17.6 w (95% CI: 15.1–18.3) in the CB group	8.6 mo, 36.9 w (95% CI: 34.1–45.6) in the CB group
NBI-3001	Weber	[60]	2003	Phase I Recurrent MGs	25/31	6–9 μg/ml × 15–100 ml 6.9–17.3 μl/min × 4 d Tumor	6 μg/ml × 40 ml	Neurological symptoms	22/31 partial or extensive tumor necrosis on MRI	5.8 mo in GBM, 8.2 in all patients
Tf-CRM107	Laske	[62]	1997	Phase I Recurrent malignant brain tumors	10/18	0.1–3.2 μg/ml × 5–180 ml 4–10 μl/min × 2–16 d Tumor	0.67 μg/ml × 40 ml	Peritumoral injury	9/15 partial and complete responses	9.5 mo 41 w (95% CI: 21.3–70.0)
	Weaver	[61]	2003 Tf-CRM107	Phase II Recurrent MGs	44 (unreported number of GBM)	0.67 μg/ml × 40 ml 3.3–6.6 μl/min × 4–5 d Tumor		Cerebral edema	11/44 partial and complete responses	8.6 mo, 37 w (95% CI: 26–49)
TP-38	Sampson	[59]	2007	Phase I Recurrent malignant brain tumors	17/20	25–100 ng/ml × 40 ml 13.3 μl/min × 2 d Tumor	100 ng/ml × 40 ml	Fatigue, hemiparesis	2/15 partial and complete responses PFS: 3.4 mo, 14.9 w (95% CI: 4.1–45.1)	6.5 mo, 28 w (95% CI: 26.5–102.8).

mo = months, w = weeks, d = days, MG = malignant gliomas, GBM = glioblastoma multiforme, MTD = maximum tolerated dose, CI = confidence interval, PFS = progression free survival and CTV = clinical target volume.

because histology did not confirm radiological diagnosis of MG, so that 38 patients (arm A) received 5-FU + XRT, while 39 patients (arm B) received XRT only. While the incidence of grades 3–4 neurologic disorders and deficits was 3–16% in arm A, no grades 3–4 neurological toxicity occurred in arm B. Besides absence of significance in the trend of survival since diagnosis favoring arm A vs. arm B (15.2 months vs. 13.5 months), a number of biases, such as the open-label nature of the trial and the different prevalence of GBM between the two arms (71% in arm A vs. 87% in arm B), make such an advantage in survival of little valuable information [20].

In other clinical trials, implantation of 6-carboxylcellulose polymers delivering 45 mg of radiosensitizing cisplatin in 21 primary GBM patients was well tolerated and associated with a better survival with respect to a control group of 11 primary GBM patients (427.5 days vs. 211.0 days, $p < 0.01$) [22], while 22 recurrent GBM patients safely received a mixture of Surgifoam gel and mitoxantrone applied into the surgical cavity [23]. Unlike Gliadel®, these two studies were not supported by the necessary preclinical background to be satisfactorily informative about drug penetration in the cerebral tissue.

3.3. Mitoxantrone and other chemotherapics

Mitoxantrone has proven to reach adequate concentrations in human intracerebral tumors after intravenous administration [42] and is reported to be active against malignant glial cells [43]. In a retrospective study [43], 276 patients with primary GBM (homogenous as to previous radiotherapy and chemotherapy treatment, Karnofsky Performance Status (KPS) >70) were treated at recurrence either with systemic temozolomide only (group A, 161 patients), or with systemic temozolomide + surgical operation (group B, 50 patients) or with surgical operation + systemic temozolomide + local delivery of mitoxantrone (group C, 65 patients). 200 mg/m^2 of temozolomide and 4 mg of mitoxantrone were respectively delivered on day 1 through day 5 and on days 1 and 5 of a 28-day cycle. Mitoxantrone was injected via a Rickham/Ommaya reservoir in the SCRC. No additional systemic side effect was caused by mitoxantrone. The only serious adverse effect attributable to local treatment was skin infection or decubitus which occurred in 8 of 65 patients (12.3%). Median survival after recurrence was 5 months in group A, 8 months in group B and 11 months in group C (A vs. B vs. C, $p < 0.001$). Even though groups were rather homogenous with respect to major prognostic factors like histology, age, KPS and previous treatment, the lack of randomization and the retrospective nature represent the major drawbacks of this study. In fact, patients of group A were not operated upon because they were judged to be inoperable (e.g. because of multifocal disease), while patients of group C were given local treatment on the basis of their compliance. Such a selection process is highly biasing. This study provides strong evidence about the safety of combined local mitoxantrone and systemic temozolomide. It does justify a phase III trial, but it cannot draw any definite conclusion about the effectiveness of this approach [43]. In three small trials, doxorubicin [44], liposomial doxorubicin (Caelyx®) [45] and bleomicyn [12] were respectively administered via Ommaya/modified Ommaya reservoirs in the SCRC of 10, 12 and 9 patients with recurrent MGs, mainly GBM. The reported survival after recurrence was 13, 9.3 and 6 months, respectively. Headache [44], reservoir-related infections [45], and neurologic symptoms [12] were the most frequently side effects reported.

In these four studies, surgical debulking was required for local therapy. CED can be employed also when no tumor resection is possible. In two similar trials, paclitaxel was delivered intratumorally via CED in 15 patients [35] and 8 patients [26] with recurrent MGs. Convection was monitored by DW-MRI. Besides aseptic meningitis occurring in 40% of patients due to paclitaxel leak, the two important findings of the first study were a response rate of 73% and the effectiveness of DW-MRI monitoring, which identified inadequate delivery in two patients [35]. The second study did not report such a high rate of aseptic meningitis, possibly because of lower administered doses of paclitaxel, but skin necrosis due to paclitaxel outflow occurred in the first two patients. Of note, it appeared that sealing the burr hole with bone wax did eliminate the problem and also improved the Vd in the remaining 6 patients [26]. Follow-up was conducted with MRI in these two studies, although MRI specificity might not be satisfactory after CED, due to CED-related contrast-enhancing radiographic changes. A small study showed that O-(2-[18F]fluoroethyl)-L-tyrosine (FET) PET can be advantageously used during follow-up after CED of paclitaxel in support of MRI findings [46].

4. Radioactive agents

4.1. Anti-tenascin antibodies

Murine monoclonal antibody ^{131}I-81C6 is directed against tenascin, a glycoproteic antigen ubiquitously present in MGs, but not in normal brain tissue [47,48]. It showed promising activity in preclinical studies and a good safety profile in phase I dose-finding trials [47,48]. In two phase II trials, ^{131}I-m81C6 was administered in the SCRC, via a Rickham reservoir, after gross total resection of newly diagnosed (27 GBM out of 33) [47] and recurrent (33 GBM and 1 gliosarcoma out of 43) [48] MGs at fixed doses of 120 and 100 mCi, respectively. On the basis of MRI and SPECT results, these two studies calculated the mean radiation dose absorbed to the 2 cm-thick SCRC interface to be 48 Gy (range, 24–116 Gy) [47] and 46 Gy (range, 18–186 Gy) [48], respectively. Severe, transient hematologic and neurologic toxicity was respectively reported in 27% and 9% [47] and in 21% and 12% [48] of the population, while median overall survival was 86.7 weeks or 20.2 months and 68.6 weeks or 16 months, respectively, in newly diagnosed and recur-

rent MGs. Five patients (15%) [47] and 1 patient (2%) [48] exhibited irreversible severe treatment-related neurotoxicity, which may have been related to the wide range of absorbed dosage after administration of a fixed dose. In order to deliver a boost of exactly 44 Gy, which appears to optimally balance risk of radionecrosis with that of recurrence, a phase I trial administered a patient-specific dose of ^{131}I-m81C6 [49]. Of 21 newly diagnosed MGs (15 GBM and 6 AA), 20 received a boost of 44 ± 4 Gy in the 2 cm thick wall of the SCRC and none of them showed severe, irreversible neurologic toxicity. Interestingly, in this trial survival since diagnosis was 90.6 weeks or 20.9 months for GBM patients [49].

Humanized, chimeric monoclonal antibody ^{131}I-81C6 caused a rate of severe treatment-related hematologic toxicity higher than expected (36% of 41 patients with newly diagnosed and recurrent MG), potentially due to its higher stability as compared to murine 81C6 [50]. No such events were reported in 19 newly diagnosed MGs treated with the same ch81C6 conjugated to ^{211}At, possibly due to shorter particle penetration and half-life of α emitter ^{211}At with respect to β emitter ^{131}I [51].

^{131}I and ^{90}Y are both β emitters, but ^{90}Y displays some favorable characteristics with respect to^{131}I, like a greater radiation penetration depth (12 mm vs. 3 mm) and no emission of γ rays. Local injections of murine anti-tenascin antibodies radiolabeled either with ^{131}I or with ^{90}Y were respectively performed in 91 (74 GBM) and 43 (35 GBM) MG patients (with newly diagnosed or recurrent disease) at a mean dose of 45 and 20 mCi, respectively. In both series of patients, no relevant treatment-related toxicity was reported. Survival since diagnosis was similar in GBM patients treated either with the ^{131}I or with the ^{90}Y labeled antibody (19 and 20 months, respectively) [52]. In a smaller study, 26 recurrent GBM patients received multiple local injections of ^{90}Y anti-tenascin BC4 antibodies in the SCRC at a dose of 5–25 mCi, concomitantly with 3 courses of systemic PCV (procarbazine, lomustine, and vincristine) chemotherapy. Of note, 20 patients also received concomitant local injections of 4 mg of mitoxantrone, with an excellent safety profile of this triple combination and a promising survival from diagnosis of 20 months [53].

4.2. COTARA and others

Cotara is a ^{131}I-labeled chimeric monoclonal antibody against a universal, non-soluble, non-diffusible intracellular antigen, which is abundantly present in the necrotic core of malignant solid tumors. Once bound to the histone H1 complexed to deoxyribonucleic acid antigen, it delivers a cytotoxic radiation dose to contiguous tumor cells [54]. Fifty-one inoperable patients with newly diagnosed and recurrent MGs received Cotara via CED in a phase I/II trial. In the phase I part of the trial, doses of 1 and 1.5 mCi/cm^3 were safely administered to MRI target volume in 12 patients. In the phase II part of the trial, 39 patients received one or two infusions at doses of 1 or 1.5 mCi/cm^3. Importantly, the majority of patients received 90–110% of the planned total activity, which was 34.9 ± 23.3 mCi and 35.4 ± 30.5 mCi for the first and second infusion, respectively. The main finding of the study was the excellent safety profile of Cotara, with only 4–6% and 2–4% of patients showing grades 3–4 neurologic and cognitive symptoms, respectively. Data about SPECT Vd and population survival were promising (12 recurrent GBM patients had a survival after recurrence of 37.9 weeks), but it was of limited significance because it was only in a few, selected patients [54]. DOTAGA-SP, a vector against neurokinin type-1 receptor (NK1R), was investigated in a preclinical/clinical study. In the preclinical part, NK1R was identified in 32 of 34 glioblastoma specimens. In the clinical part, ^{90}Y-DOTAGA-SP was safely delivered at a mean dose of 118 mCi via intracavitary or intratumoral injection. Five of 14 GBM patients reported an improvement of impaired neurologic functions. Of note, DOTACA-SP was also labeled with β emitter ^{177}Lu and α emitter ^{213}Bi to be administered in critically located lesions, because of their minor radiation penetration depth (1.5 and 0.06 mm, respectively), in comparison to that of ^{90}Y (12 mm) [55].

A clinical study in 9 recurrent MG patients showed that the monoclonal antibody, recognizing the Epidermal growth factor receptor (EGFR), nimotuzumab, radiolabeled with emitter ^{188}Re could be safely locally delivered at a MTD (maximum total dosage) of 10 mCi, with low radioactivity distribution in the rest of the body [56].

5. Receptor targeted toxins

5.1. IL-13 and EGF receptors

Cintredekin besudotox (CB) is composed of human IL-13 and truncated *Pseudomonas* exotoxin and binds to IL-13 receptor expressed on GBM cells. After surgical tumor excision, 51 patients with recurrent MGs (46 GBM) received intraparenchymal CED of CB in the walls of the SCRC. Treatment was well tolerated and potentially effective with the main grades 3–4 toxicity being hemiparesis (12% of patients) and a median survival after recurrence of 45.9 weeks. Parney's scoring system [57], which can help discern reactive CED-related changes from recurrence, was employed to score radiographic changes on MRI. Grade IV changes were seen at doses higher than MTD [58]. TP-38 is composed of truncated *Pseudomonas* exotoxin and transforming growth factor-α, which binds to EGF receptor expressed by GBM cells. In a phase I study, this toxin was safely administered via CED to 20 patients with recurrent malignant brain tumors (17 GBM). Two patients suffered dose-limiting toxicity, but 13 of 15 patients with residual tumor showed no radiographic response, possibly due to low Vd in the brain [59]. In fact, besides treatment tolerability, the major finding of these two reports is the high rate of ineffective delivery, which was documented by SPECT in 42% and 81% of catheters, respectively in the first [58] and in the second [59] study.

The PRECISE trial randomized 294 recurrent GBM patients in a 2:1 ratio to either CED of CB in the walls of the SCRC or Gliadel implantation in the SCRC after tumor gross total resection. Median time to progression was 17.6 weeks (95% CI: 15.1–18.3) in the CB group, while median survival was 36.9 weeks (95% CI: 34.1–45.6) and did not differ significantly from median survival in the Gliadel group. Correct catheter placement and investigator experience did not appear to influence overall survival. Ineffective drug distribution was a likely cause of failure of this trial. As discussed before, the iPlan Flow software might dramatically improve coverage of the target volume and its use in large, prospective trials is warranted [9].

5.2. Transferrin and IL-4 receptors

On the basis of high IL-4 receptor expression on glioma cells, 31 patients with recurrent MGs (25 GBM, 6 AA) received CED of NBI-3001, an IL-4 receptor targeting toxin composed of circularly permuted IL-4 and truncated *Pseudomonas* exotoxin. Drug-related grades 3–4 toxicity, which was mainly neurological, was reported in 39% of patients in all dose groups, while median survival after treatment was 8.2 and 5.8 months in the whole population and in GBM patients, respectively. No direct data are available about the rate of ineffective CED infusions, although one patient developed a chemical meningitis, plausibly due to toxin leak into the subarachnoid space. About 70% of all tumors showed a partial or total necrosis on MRI, but the incidence of severe toxicity was 22% even at MTD. Severe toxicity could be related to necrosis-induced increasing intracranial pressure and diminished by scheduling a necrosectomy after CED [60].

Tf-CRM107 (TransMID^{TM}) is composed of a modified diphtheria toxin on human transferrin, which is unable to bind non-specifically to human cells. In light of high expression levels of transferrin receptors on malignant glial cells, a phase I study was conducted in 18 patients with malignant brain tumors (10 recurrent GBM), who received intratumoral CED of TransMID. Of 15 evaluable patients, 5 presented signs of peritumoral brain injury, at doses higher than MTD, while 9 presented partial or complete response [61]. A subsequent phase II trial, administering Tf-CRM107 to 44 patients with recurrent MGs, reported response rate of 39%, with the main toxicity represented by manageable cerebral edema in 11% of the patients [62]. These promising results were not confirmed in a phase III trial, which compared intratumoral TransMID vs. systemic chemotherapy in patients with recurrent or progressive GBM. This study was withdrawn early due to lack of efficacy [63].

6. Concluding remarks

We have shown that, although a wide variety of therapeutic agents have been tested, Gliadel is the sole local treatment with solid evidence of effectiveness, as it provided a statistically significant prolongation in survival (about 2 months) in newly diagnosed MG [37] and recurrent [36] GBM patients, in comparison to placebo. Since 2008, the National Comprehensive Cancer Network Practice Guidelines in Oncology have recommended the combination of Gliadel followed by radiation, with concurrent adjuvant temozolomide in patients with newly diagnosed MGs, despite lack of evidence from a randomized, controlled trial. Gliadel is well tolerated and does not require any particular expertise or compliance, but it is quite expensive and it needs invasive surgery to be implanted. On the contrary, subcutaneous reservoirs are very versatile and can be easily and repeatedly refilled for intracavitary delivery of various agents. Local delivery via Rickham/Ommaya reservoirs of mitoxantrone [43] in recurrent MGs and of radiolabeled anti-tenascin antibodies [47–53] in both newly diagnosed and recurrent MGs has shown very promising results, in terms of both efficacy and safety, and there is sufficient evidence to recommend a phase III trial.

Unlike Ommaya/Rickham reservoirs, CED does not require surgical tumor excision to be performed, in that it can deliver therapeutic agents directly into brain or tumor tissues. In the reviewed articles, CED was employed for intratumoral administration of various agents, mainly paclitaxel [26,35] and high molecular weight targeted toxins [58–63]. These agents show in vitro activity on malignant glial cells, but they cannot be effectively delivered with diffusion-based techniques. In a small study [35], CED of paclitaxel showed a response rate of 73%, but it also caused cremophor-related aseptic meningitis, which could be prevented by using the newer albumin-paclitaxel conjugated nab® (nanoparticle albumin-bound) technology Abraxane® [64]. Furthermore, Abraxane albumin could be radiolabeled with ^{123}I or ^{124}I and used to perform SPECT. Local delivery of targeted toxins allows for molecular and anatomical targeting at the same time, with the possibility of increased safety and effectiveness. The promising results from phases I and II trials were confirmed by two large phase III trials on CB [9] and TransMid [63]. Ineffective delivery is considered a probable cause of these failures [9]. Although it is clear that CED holds a tremendous potential, it is also clear that, due to its high complexity, it can be difficult to standardized in order to provide a predictable Vd. Catheter trajectory, which must be appropriate for an effective delivery, is generally determined following simple rules and guidelines. The computerized program by Brain Lab [9,30] might represent a powerful tool for correct catheter placement, but it can be employed for intraparenchymal delivery only, while most of the CED trials have adopted intratumoral administration.

Multimodality treatment is the mainstay of therapy of MGs. It is therefore noteworthy that many of the reviewed articles have showed that intracerebral chemotherapy can be safely combined with surgery, radiotherapy and systemic chemotherapy. Moreover, agents like radioactive antibodies and mitoxantrone can also be safely combined for intracavi-

tary delivery [54], showing the feasibility of combined local delivery of these or possibly other agents. Unfortunately, while no large, randomized, controlled trial has been conducted or is underway on mitoxantrone or radioactive agents, in spite of sufficient evidence to recommend a phase III trial, two phase III trials on CED have been prematurely carried out and they both failed because the aforementioned CED technical hindrances are yet to be resolved.

Search criteria

Three groups of words were defined. Group A: 'glioma', 'gliomas', 'glioblastoma'. Group B: 'local', 'loco-regional', 'intratumoral', 'intratumoral', 'intracerebral', 'intraparenchymal', 'intralesional', 'intracavitary', 'interstitial', 'polymer', 'antitenascin'. Group C: 'convection enhanced', 'Gliadel', 'carmustine wafers'. Our search criteria on PUBMED included articles presenting at least one word of group A and at least one word of group B in any field and articles with at least one word of group C in any field. Only human studies written in English and published from January 1994 to December 2009 were evaluated. Originality, sample numerosity and publication date defined articles' priority. Articles quoted by reviewed articles and abstracts from relevant US and European cancer meetings were also considered.

Contributors

Conception and design: Carlo Buonerba and Giuseppe Di Lorenzo.
Provision of study materials: Carlo Buonerba, Giuseppe Di Lorenzo, Pio Conti and Alfredo Marinelli.
Collection and assembly of data: Carlo Buonerba, Giuseppe Di Lorenzo, Piera Federico, Giovannella Palmieri, Pio Conti, Gianfranco Peluso, Martina Imbimbo, Alfredo Marinelli, Sabino De Placido, and John Sampson.
Data analysis and interpretation: Carlo Buonerba, Giuseppe Di Lorenzo and Sabino de Placido.
Manuscript writing: Carlo Buonerba and Giuseppe Di Lorenzo.
Revision of the paper: John Sampson.
Final approval of manuscript: all authors.

Conflict of interest

The authors have no conflict of interest to declare.

Funding

No financial support of any kind was obtained for the writing of this review.

Reviewers

Hans Ericson, M.D., Ph.D., Clinique de Genolier, Department of Neurosurgery, CH-1272 Genolier, Switzerland.

Laura A. Johnson, Ph.D., Duke University Medical Center, Duke Brain Tumor Immunotherapy Program, Preston Robert Tisch Brain, Tumor Center, Durham, NC 27710, United States.

Acknowledgements

The authors wish to thank Prof. Vincenzo Esposito, from the Department of Neurological Sciences of University of Rome "La Sapienza", for his support and encouragement during the writing of this article.

References

[1] Stupp R, Roila F, ESMO Guidelines Working Group. Malignant glioma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20(Suppl.):S126–8.
[2] Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96.
[3] Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. Neurology 1980;30:907–11.
[4] Nieder C, Grosu AL, Molls M. A comparison of treatment results for recurrent malignant gliomas. Cancer Treatment Rev 2000;26:397–409.
[5] Walter KA, Tamargo RJ, Olivi A, Burger PC, Brem H. Intratumoral chemotherapy. Neurosurgery 1995;37:1128–45.
[6] Chamberlain MC. Combined-modality treatment of leptomeningeal gliomatosis. Neurosurgery 2003;52:324–9.
[7] Misra A, Ganesh S, Shahiwala A, Shah SP. Drug delivery to the central nervous system: a review. J Pharm Pharm Sci 2003;6:252–73.
[8] Bobo RH, Laske DW, Akbasak A, Morrison PF, Dedrick RL, Oldfield EH. Convection-enhanced delivery of macromolecules in the brain. Proc Natl Acad Sci USA 1994;91:2076–80.
[9] Sampson JH, Archer G, Pedain C, et al. Poor drug distribution as a possible explanation for the results of the PRECISE trial. J Neurosurg 2009 [December 18; Epub ahead of print].
[10] Engelhard HH. The role of interstitial BCNU chemotherapy in the treatment of malignant glioma. Surg Neurol 2000;53:458–64.
[11] Berweiler U, Krone A, Tonn JC. Reservoir systems for intraventricular chemotherapy. J Neurooncol 1998;38:141–3.
[12] Patchell RA, Regine WF, Ashton P, et al. A phase I trial of continuously infused intratumoral bleomycin for the treatment of recurrent glioblastoma multiforme. J Neurooncol 2002;60:37–42.
[13] Jain JP, Modi S, Domb AJ, Kumar N. Role of polyanhydrides as localized drug carriers. J Control Release 2005;103:541–63.
[14] Brem H, Kader A, Epstein JI, et al. Biocompatibility of a biodegradable, controlled-release polymer in the rabbit brain. Sel Cancer Ther 1989;5:55–65.
[15] Sipos EP, Tyler B, Piantadosi S, Burger PC, Brem H. Optimizing interstitial delivery of BCNU from controlled release. Cancer Chemother Pharmacol 1997;39:383–9.
[16] Bidros DS, Vogelbaum MA. Novel drug delivery strategies in neurooncology. Neurotherapeutics 2009;6:539–46.
[17] Domb AJ, Rock M, Perkin C, et al. Excretion of a radiolabelled anticancer biodegradable polymeric implant from the rabbit brain. Biomaterials 1995;16:1069–72.

[18] Brem H, Tamargo RJ, Olivi A, et al. Biodegradable polymers for controlled delivery of chemotherapy with and without radiation therapy in the monkey brain. J Neurosurg 1994;80:283–90.
[19] Sawyer AJ, Piepmeier JM, Saltzman WM. New methods for direct delivery of chemotherapy for treating brain tumors. Yale J Biol Med 2006;79:141–52.
[20] Menei P, Capelle L, Guyotat J, et al. Local and sustained delivery of 5-fluorouracil from biodegradable microspheres for the radiosensitization of malignant glioma: a randomized phase II trial. Neurosurgery 2005;56:242–8.
[21] Roullin VG, Deverre JR, Lemaire L, et al. Anti-cancer drug diffusion within rat brain tissue: an experimental study using [3H]-(6)-5-fluorouracil-loaded PLGA microspheres. Eur J Pharm Biopharm 2002;53:293–9.
[22] Sheleg SV, Korotkevich EA, Zhavrid EA, et al. Local chemotherapy with cisplatin-depot for glioblastoma multiforme. J Neurooncol 2002;60:53–9.
[23] Ferroli P, Broggi M, Franzini A, et al. Surgifoam and mitoxantrone in the glioblastoma multiforme postresection cavity: the first step of locoregional chemotherapy through an ad hoc-placed catheter: technical note. Neurosurgery 2006;59:E433–4.
[24] Raghavan R, Brady ML, Rodríguez-Ponce MI, Hartlep A, Pedain C, Sampson JH. Convection-enhanced delivery of therapeutics for brain disease, and its optimization. Neurosurg Focus 2006;20:E12.
[25] Allard E, Passirani C, Benoit JP. Convection-enhanced delivery of nanocarriers for the treatment of brain tumors. Biomaterials 2009;30:2302–18.
[26] Tanner PG, Holtmannspötter M, Tonn JC, Goldbrunner R. Effects of drug efflux on convection-enhanced paclitaxel delivery to malignant gliomas: technical note. Neurosurgery 2007;61:E880–2.
[27] Varenika V, Dickinson P, Bringas J, et al. Detection of infusate leakage in the brain using real-time imaging of convection-enhanced delivery. J Neurosurg 2008;109:874–80.
[28] Sampson JH, Brady ML, Petry NA, et al. Intracerebral infusate distribution by convection-enhanced delivery in humans with malignant gliomas: descriptive effects of target anatomy and catheter positioning. Neurosurgery 2007;60:S89–98.
[29] Fiandaca MS, Forsayeth JR, Dickinson PJ, Bankiewicz KS. Image-guided convection-enhanced delivery platform in the treatment of neurological diseases. Neurotherapeutics 2008;5:123–7.
[30] Sampson JH, Raghavan R, Brady ML, et al. Clinical utility of a patient-specific algorithm for simulating intracerebral drug infusions. Neuro Oncol 2007;9:343–53.
[31] Lonser RR, Warren KE, Butman JA, et al. Real-time image-guided direct convective perfusion of intrinsic brainstem lesions. Technical note. J Neurosurg 2007;107:190–7.
[32] Ding D, Kanaly CW, Bigner DD, et al. Convection-enhanced delivery of free gadolinium with the recombinant immunotoxin MR1-1. J Neurooncol 2009 [November; Epub ahead of print].
[33] Voges J, Reszka R, Gossmann A, et al. Imaging-guided convection-enhanced delivery and gene therapy of glioblastoma. Ann Neurol 2003;54:479–87.
[34] Sampson JH, Raghavan R, Provenzale JM, et al. Induction of hyperintense signal on T2-weighted MR images correlates with infusion distribution from intracerebral convection-enhanced delivery of a tumor-targeted cytotoxin. Am J Roentgenol 2007;188(March):703–9.
[35] Lidar Z, Mardor Y, Jonas T, et al. Convection-enhanced delivery of paclitaxel for the treatment of recurrent malignant glioma: a phase I/II clinical study. J Neurosurg 2004;100:472–9.
[36] Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. Lancet 1995;345:1008–12.
[37] Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro Oncol 2003;5:79–88.
[38] Quinn JA, Jiang SX, Carter J, et al. Phase II trial of Gliadel plus O6-benzylguanine in adults with recurrent glioblastoma multiforme. Clin Cancer Res 2009;15:1064–8.
[39] La Rocca RV, Mehdorn HM. Localized BCNU chemotherapy and the multimodal management of malignant glioma. Curr Med Res Opin 2009;25:149–60.
[40] La Rocca R, Vitaz TW, Villanueva W, et al. A phase 2 study of multi modal therapy with surgery, carmustine wafer, radiation therapy, and temozolomide in patients with newly diagnosed supratentorial malignant gliomas [abstract]. Neuro Oncol 2008;10:1123.
[41] McGirt MJ, Than KD, Weingart JD, et al. Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. J Neurosurg 2009;110:583–8.
[42] Green RM, Stewart DJ, Hugenholtz H, Richard MT, Thibault M, Montpetit V. Human central nervous system and plasma pharmacology of mitoxantrone. J Neurooncol 1988;6:75–83.
[43] Boiardi A, Silvani A, Eoli M, et al. Treatment of recurrent glioblastoma: can local delivery of mitoxantrone improve survival? J Neurooncol 2008;88(May):105–13.
[44] Voulgaris S, Partheni M, Karamouzis M, Dimopoulos P, Papadakis N, Kalofonos HP. Intratumoral doxorubicin in patients with malignant brain gliomas. Am J Clin Oncol 2002;25:60–4.
[45] Boiardi A, Eoli M, Salmaggi A, et al. New approach in delivering chemotherapy: locoregional treatment for recurrent glioblastoma (rGBM). J Exp Clin Cancer Res 2003;22:S123–7.
[46] Pöpperl G, Goldbrunner R, Gildehaus FJ, et al. O-(2-[18F]fluoroethyl)-L-tyrosine PET for monitoring the effects of convection-enhanced delivery of paclitaxel in patients with recurrent glioblastoma. Eur J Nucl Med Mol Imaging 2005;32:1018–25.
[47] Reardon DA, Akabani G, Coleman RE, et al. Phase II trial of murine (131)I-labeled antitenascin monoclonal antibody 81C6 administered into surgically created resection cavities of patients with newly diagnosed malignant gliomas. J Clin Oncol 2002;20:1389–97.
[48] Reardon DA, Akabani G, Coleman RE, et al. Salvage radioimmunotherapy with murine iodine-131-labeled antitenascin monoclonal antibody 81C6 for patients with recurrent primary and metastatic malignant brain tumors: phase II study results. J Clin Oncol 2006;24:115–22.
[49] Reardon DA, Zalutsky MR, Akabani G, et al. A pilot study: 131I-antitenascin monoclonal antibody 81c6 to deliver a 44-Gy resection cavity boost. Neuro Oncol 2008;10:182–9.
[50] Reardon DA, Quinn JA, Akabani G, et al. Novel human IgG2b/murine chimeric antitenascin monoclonal antibody construct radiolabeled with 131I and administered into the surgically created resection cavity of patients with malignant glioma: phase I trial results. J Nucl Med 2006;47:912–8.
[51] Zalutsky MR, Reardon DA, Akabani G, et al. Clinical experience with alpha-particle emitting ^{211}At: treatment of recurrent brain tumor patients with ^{211}At-labeled chimeric antitenascin monoclonal antibody 81C6. J Nucl Med 2008;49:30–8.
[52] Riva P, Franceschi G, Riva N, Casi M, Santimaria M, Adamo M. Role of nuclear medicine in the treatment of malignant gliomas: the locoregional radioimmunotherapy approach. Eur J Nucl Med 2000;27:601–9.
[53] Boiardi A, Bartolomei M, Silvani A, et al. Intratumoral delivery of mitoxantrone in association with 90-Y radioimmunotherapy (RIT) in recurrent glioblastoma. J Neurooncol 2005;72:125–31.
[54] Patel SJ, Shapiro WR, Laske DW, et al. Safety and feasibility of convection-enhanced delivery of Cotara for the treatment of malignant glioma: initial experience in 51 patients. Neurosurgery 2005;56:1243–52.
[55] Kneifel S, Cordier D, Good S, et al. Local targeting of malignant gliomas by the diffusible peptidic vector 1,4,7,10-tetraazacyclododecane-1-glutaric acid-4,7,10-triacetic acid-substance p. Clin Cancer Res 2006;12:3843–50.
[56] Torres LA, Coca MA, Batista JF, et al. Biodistribution and internal dosimetry of the ^{188}Re-labelled humanized monoclonal antibody anti-epidemal growth factor receptor, nimotuzumab, in the locoregional treatment of malignant gliomas. Nucl Med Commun 2008;29:66–75.

[57] Parney IF, Kunwar S, McDermott M, et al. Neuroradiographic changes following convection-enhanced delivery of the recombinant cytotoxin interleukin 13-PE38QQR for recurrent malignant glioma. J Neurosurg 2005;102:267–75.
[58] Kunwar S, Prados MD, Chang SM, et al. Direct intracerebral delivery of cintredekin besudotox (IL13-PE38QQR) in recurrent malignant glioma: a report by the Cintredekin Besudotox Intraparenchymal Study Group. J Clin Oncol 2007;25:837–44.
[59] Sampson JH, Akabani G, Archer GE, et al. Intracerebral infusion of an EGFR-targeted toxin in recurrent malignant brain tumors. Neuro Oncol 2008;10:320–9.
[60] Weber F, Asher A, Bucholz R, et al. Safety, tolerability, and tumor response of IL4-*Pseudomonas* exotoxin (NBI-3001) in patients with recurrent malignant glioma. J Neurooncol 2003;64:125–37.
[61] Weaver M, Laske DW. Transferrin receptor ligand-targeted toxin conjugate (Tf-CRM107) for therapy of malignant gliomas. J Neurooncol 2003;65:3–13.
[62] Laske DW, Youle RJ, Oldfield EH. Tumor regression with regional distribution of the targeted toxin TF-CRM107 in patients with malignant brain tumors. Nat Med 1997;3:1362–8.
[63] Study of therapy with TransMID^{TM} compared to best standard of care in patients with glioblastoma multiforme. Available at: http://clinicaltrials.gov/ct2/show/NCT00083447 [Accessed 22.12.09].
[64] Kratz F. Albumin as a drug carrier: design of prodrugs, drug conjugates and nanoparticles. J Control Release 2008;132:171–83.

Biography

Giuseppe Di Lorenzo is Oncologist at the University "Federico II", Department of Medical Oncology, Napoli, Italy; Ph.D. in Molecular Oncology and Endocrinology. He is Chief of Campania Younger Oncologists Association (AGOC). His main field of research is genitourinary cancer. He is co-author of several books and external clinical reviewer for various journals, including the Lancet, the Lancet Oncology, European Urology and Critical reviews in Oncology/Hematology. He is author of 94 full papers with overall Impact factor of 400.