Review Article

Convection-enhanced Drug Delivery for Glioblastoma: A Systematic Review Focused on Methodological Differences in the Use of the Convection-enhanced Delivery Method

Bo Halle[1,2], Kristian Mongelard[1,2], Frantz Rom Poulsen[1,2]

[1]Department of Neurosurgery, Odense University Hospital and BRIDGE - Brain Research - Inter-Disciplinary Guided Excellence, [2]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

Abstract

Glioblastoma (GBM) is a leading cause of brain cancer-related death. The blood–brain barrier (BBB) prevents the transport of most systemic delivered molecules to the brain. This constitutes a major problem in the therapy of brain tumors. In the last decade, numerous different drug-delivery approaches have been developed to overcome the BBB. The objective of this study is to provide an overview of the methodological aspects used in all preclinical and clinical studies published from 2011 to 2016 where convection-enhanced delivery (CED) was used for drug delivery in the treatment of GBM. A systematic review of English articles published in the past 5 years was undertaken using PubMed and Embase. The search terms (brain tumor [MeSH Terms]) AND (CED OR convection enhanced delivery) were used in PubMed and a similar search was carried out in Embase using their "multi-field search." All studies using CED on an intracranial GBM model were included. The search resulted in 151 hits after duplicates were removed. In total, 30 studies were included in the review. Of these, two publications studied the technical aspects of the CED method. Furthermore, only one study was a clinical study. The research field is focused on preclinical drug development trials and less emphasis is placed on the CED technique itself. However, it is important that future studies focus on establishing optimal protocols for the use of CED in rodents as well as for big brain models to be able to use the CED method in patients with GBM.

Keywords: *Blood–brain barrier, brain tumor, convection-enhanced delivery, glioblastoma, oncology*

Introduction

Glioblastoma (GBM) is one of the most malignant brain tumors and increases in frequency with age. GBM remains incurable, and despite trimodal therapy, the median survival is only 14–20 months. Combining surgical resection, external radiation, and chemotherapy has little effect.[1,2]

Two important factors account for the lack of effectiveness: the inherent ability of the GBM tumor to infiltrate deep into surrounding tissue, which makes complete resection impossible,[3] and the ineffectiveness of systemic drug-delivery due to the blood–brain barrier (BBB). Furthermore, the molecular characteristics of available chemotherapeutic agents (polar and with a high molecular weight) make penetration across the BBB even more challenging.[4]

To overcome the challenges of the BBB, Bobo *et al*.[4] proposed the use of convection-enhanced delivery (CED). CED creates fluid convection by maintaining the pressure gradient throughout the infusion. This greatly enhances the distribution of the desired molecule.[4] Convection through CED differs from simple diffusion. Simple diffusion is the passive movement of solute from a high concentration to a lower concentration, whereas the movement created by CED is due to the positive pressure created by the pump.

Despite the fact that CED was already described back in 1994[4] and has been used in numerous clinical trials since,[5-13] no drugs have yet been approved for administration by CED. Moreover, only one Phase III trial has been completed,[12] and this failed probably due to insufficient drug distribution.[14] This clearly shows that CED is not a simple technique to apply and that not all drugs convect just because they are infused into the brain parenchyma. Essential aspects to consider are catheter design, number of catheters used and their

How to cite this article: Halle B, Mongelard K, Poulsen FR. Convection-enhanced drug delivery for glioblastoma: A systematic review focused on methodological differences in the use of the convection-enhanced delivery method. Asian J Neurosurg 2019;14:5-14.

Address for correspondence:
Dr. Bo Halle,
Department of Neurosurgery,
Odense University Hospital,
Sdr. Boulevard 29,
5000 Odense, Denmark.
E-mail: bo.halle@rsyd.dk

Access this article online

Website: www.asianjns.org

DOI: 10.4103/ajns.AJNS_302_17

Quick Response Code:

placement, infusion rate and start-up infusion protocol, duration of infusion, type of drug infused (cell affinity, drug size and charge, lipo-/hydro-philic), potential drug encapsulation, and importantly, which method to use to evaluate drug distribution.

In this systematic review, our objective was to provide an overview of the methodological aspects listed above in all preclinical and clinical studies published from 2011 to 2016 where CED was used for drug administration in the treatment of GBM.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses was used. The ethical committee at our department approved the study.

Articles in English published in the period from October 30, 2011, to October 30, 2016, registered in Embase or PubMed were included in this review. In addition, the reference lists were read to ensure that all relevant studies were included.

The search term (brain tumor [MeSH Terms]) AND (CED OR convection enhanced delivery) was used in PubMed. A similar search was carried out for Embase using their multi-field search tool.

No limits were applied to the search on PubMed and Embase. The last search was carried out on October 30, 2016.

Data relating to the CED methodology used in each of the publications were extracted and the following data were registered: What type of agent was infused? What tumor cell line was used? What type and how many catheters were used for the infusion? How much was infused and at what flow rate? Did the subjects experience any adverse effects? Did the researchers evaluate drug distribution and if so what method was used? What type of pump was used? Where was the tip of the catheter placed?

Results

The search in PubMed and Embase resulted in 202 publications. After removing duplicates, 151 articles remained. Of the 151 articles, 97 articles were not experimental studies or were irrelevant to the subject of this review.

After assessing the 54 remaining articles, 22 were excluded because they did not use a GBM tumor model. One publication was excluded because it was only in Chinese. One article was not accessible and the author was contacted to get the full-text article. However, the author never responded. Accordingly, 30 articles were included as displayed in Figure 1, 29 were experimental animal studies and the last was a clinical, nonrandomized, and nonblinded study. The level of evidence in this review is thus level 5.

Preclinical data concerning mice and rats are listed in Tables 1 and 2, respectively. Clinical data are listed in Table 3.

Some of the studies in the present review included several experimental animal groups exposed to a variety of experimental conditions. Only data from intracranial GBM models in these studies were used.

The studies all infused different agents except for carboplatin, irinotecan and cetuximab-IONP. Each of these were used in two studies.

The noninvasive human U87-MG GBM cell line was used in 12/30 (40%) of the studies, seven of which were mice studies. The syngeneic F98 rat tumor cell line was used in 7/30 (23%) studies, followed by the human U251 GBM cell line, which was used in 3/30 (10%) studies.

Of 30 studies, 9 (30%) studies used simple cannulas with sizes varying from 22-gauge to 33-gauge. Whether these were blunt or sharp-tipped and which point style was used in the case of the latter were not disclosed. Of 30 studies, 7 (23%) studies used stepped catheters. Of 30 studies, 7 (23%) studies did not mention what type of catheter was used.

In 28/30 (93%) of the studies, only one catheter was used. Of 30 studies, 2 (7%) studies included experimental groups where up to four catheters were used.[42,44]

In 27/30 (90%) studies, the catheter was placed intratumorally. Of 30 studies, 1 (3.5%) study used both intratumoral and peritumoral catheter placement on different animal groups.[42] Of 30 studies, 2 (7%) studies did not specify where the catheter was placed.[30,37]

The infusion parameters varied between studies. Flow rate in mice ranged between 0.11 and 60 μl/h (mean 22.3 μl/h) and in rats ranged between 1 and 120 μl/h (mean 33.6 μl/h). In the human clinical trial, the flow rate was 400 μl/h (200 μl/h/catheter).

The total volume infused ranged between 5 and 126 μl (mean 43 μl) in mice and 5–1574 μl (mean 187.5 μl) in rats. In the clinical trial, a total volume of 40,000 μl was infused.

The duration of the infusions ranged between 5 min to 28 days (mean 5.4 days) in mice and 12.5 min to 31 days (mean 16 h) in rats. In the human clinical trial, the infusion lasted 100 h. All studies opted to use one infusion.

Of 30 studies, 8 (27%) studies used an internal pump. Of those, six were osmotic devices and two were iPRECIO micro-infusion pumps. The remaining 22 (73%) studies used an external pump.

Of 30 studies, 3 (10%) studies used magnetic resonance imaging (MRI) to evaluate drug distribution in the brain tissue. This was done by attaching iron oxide nanoparticles to the drug. On T2-weighted images, the particles are

Table 1: Summary of preclinical trials using mice

Author and year	Agent infused	Type of drug	Type of tumor	Adverse effects	Flow rate	Total volume infused	Duration	Number of catheters	Cannula/ catheter	Number of infusions	Pump	Catheter placement	Evaluation of convection
Bouras *et al.*, 2015[15]	Cetuximab-IONP	Nanoparticles	U87MG	No adverse effects observed	30 µL/h	10 µL9	20 min	1	Not mentioned	1	External	Intratumoral	MRI and histology
Kaluzova *et al.*, 2015[16]	Cetuximab-IONP	Nanoparticles	N08-30, U87MG, LN229	No adverse effects observed	30 µL/h	10 µL	20 min	1	22-gauge cannula	1	External	Intratumoral	MRI
Wang *et al.*, 2015[17]	Bevacizumab	No coating	U87MG, U251	Not mentioned for CED	0.11 µL/h	74 µL	28 days	1	Brain infusion kit	1	Internal (osmotic)	Intratumoral	No evaluation
Danhier *et al.*, 2015[18]	SiRNA/chitosan-LNC	Liposomal	U87MG	Not mentioned for CED	30 µL/h	60 µL	120 min	1	26-gauge cannula	1	External	Intratumoral	No evaluation
Bernal *et al.*, 2014[19]	Temozolomide-PMNP	Nanoparticles	U87MG	Local edema	*	10 µL	*	1	Stepped	1	External	Intratumoral	MRI and histology
Chen *et al.*, 2013[20]	Nanoliposomal irinotecan	Liposomal	GBM43/ SF7796	No adverse effects observed	60 µL/h	5-10 µL	5-10 min	1	Stepped	1	External	Intratumoral	Histology
Sonabend *et al.*, 2014[21]	Etoposide	No coating	Murine proneural GBM	Focal tissue damage limited the site of catheter placement	0.5 µL/h	84 µL	7 days	1	Alzet brain infusion kit 3	1	Internal (osmotic)	Intratumoral	No evaluation
Stephen *et al.*, 2014[22]	NPCP-BG-CTX	Nanoparticles	GBM6	Not mentioned for CED	60 µL/h	5 µL	5 min	1	Not mentioned	1	External	Intratumoral	Ex vivo NIRF
Zamykal *et al.*, 2015[23]	IMC-A12	IGFR target	U87MG, GS-12	No adverse effects observed	0.25 µL/h	126 µL	21 days	1	Alzet brain infusion kit II	1	Internal (osmotic)	Intratumoral	No evaluation
Suzuki *et al.*, 2014[24]	Interleukin-13 Pseudomonas exotoxin	IL-13 target	U251	No adverse effects observed	1.4 µL/h	101 µL	3 days	1	Not mentioned	1	Internal (osmotic)	Intratumoral	SPECT/CT
Shultz *et al.*, 2011[25]	177Lu-DOTA-f-Gd3N@ C80	Metallofullerene coated	U87MG	Not mentioned for CED	12 µL/h	18 µL	90 min	1	28-gauge cannula	1	External	Intratumoral	Inductively coupled plasma mass spectrometry
Weng *et al.*, 2013[26]	QD-IL, QD-L	Liposomal	U87MG, GBM37	Not mentioned	Ramped: 6>12>30> 48 µL/h	10 µL	22.5 min	1	Stepped	1	External	Intratumoral	Confocal laser-scanning microscopy and histology

MRI – Magnetic resonance imaging; SPECT – Single-photon emission computed tomography; CT – Computed tomography; NIRF – Near-infrared fluorescence; CED – Convection enhanced delivery; IGFR – Insulin-like growth factor 1 receptor; IL – Interleukin; BG – O6-benzylguanine; GBM – Glioblastoma; IONP – Iron oxide nanoparticles; LNC – Lipid-core nanocapsules; PMNP – Polymeric nanoparticle; NPCP-BG-CTX – Nanoparticle chitosan-PEG copolymer-O6-benzylguanine-chlorotoxin; IMC – A12 – cixutumumab; QD-L – Quantum dot-immunoliposome; * - Not disclosed

Table 2: Summary of preclinical trials using rats

Author and year	Agent infused	Type of drug	Type of tumor	Adverse effects	Flow rate	Total volume infused	Duration	Number of catheters	Cannula/ catheter	Number of infusions	Pump	Catheter placement	Evaluation of convection
Halle *et al.*, 2016[27]	Anti-let-7a	No coating	T87 GSC	No adverse effects observed	2 µL/h	1411-1574 µL	31 days	1	Plastics One	1	Internal (iPRECIO infusion pump)	Intratumoral	No evaluation
Mendiburu-Eliçabe and Gil-Ranedo, 2015[28]	Nanoliposomal irinotecan	Liposomal	U87MG	No adverse effects observed	30 µL/h	20 µL	40 min	1	Stepped	1	External	Intratumoral	No evaluation
Cooper *et al.*, 2015[29]	EA-human serum albumin	BBB targeting	Rat CNS-1	No adverse effects observed	120 µL/h	40 µL	20 min	1	33-gauge cannula	1	External	Intratumoral	No evaluation
Yang *et al.*, 2014[30]	Carboplatin	No coating	F98	Gliosis	20/1 µL/h	10/168 µL	30 min/ 7 days	1	Not mentioned	1	External and internal	Not mentioned	ICP-OES
Xi *et al.*, 2014[31]	Nanodiamond-doxorubicin	Nanodiamonds	U251	No adverse effects observed	Incremental: 6>12> 15 µL/h	5 µL	(10/10/8) 28 min	1	Not mentioned	1	External	Intratumoral	Fluorescent microscope
Yin *et al.*, 2013[32]	Retroviral-replicating-vector expressing cytosin deaminase	Tumor-selective RRV	U87MG	No adverse effects observed	60 µL/h	20 µL	20 min	1	Stepped	1	External	Intratumoral	Histology
Huo *et al.*, 2012[33]	Liposomal lipoplatin	Liposomal	F98	Necrosis and oedema	20 µL/h	10 µL	30 min	1	28 gauge cannula	1	External	Intratumoral	ICP-OES
Phillips *et al.*, 2012[34]	Rhenium-186 liposomes	Liposomal	U87MG	Gliosis	120 µL/h	25 µL	12,5 min	1	27-gauge cannula	1	External	Intratumoral	SPECT/CT
Xi *et al.*, 2012[35]	Vincristine	No coating	C6 rat	Minor trauma at the site of the infusion cannula	Incremental: 6>12> 15 µL/h	5 µL	(10/10/8) 28 min	1	26-gauge cannula	1	External	Intratumoral	No evaluation
Shi *et al.*, 2015[36]	Cisplatin, carboplatin, and lipoplatin	Liposomal	F98	Not mentioned	30 µL/h	10 µL	20 min	1	33-gauge cannula	1	External	Intratumoral	No evaluation
Zhang *et al.*, 2016[37]	SN-38-loaded polymeric micelles	Liposomal	U87MG	Not mentioned for CED	Incremental: 12>30> 48 µL/h	20 µL	(15/10/15) 40 min	1	Stepped	1	External	Not mentioned	Histology

Contd...

Table 2: Contd...

Author and year	Agent infused	Type of drug	Type of tumor	Adverse effects	Flow rate	Total volume infused	Duration	Number of catheters	Cannula/ catheter	Number of infusions	Pump	Catheter placement	Evaluation of convection
Hiramatsu *et al*., 2015[38]	Tetrakis chlorin	No coating	F98	Not mentioned	8 µL/h	192 µL	24 h	1	ALZET Brain Infusion Kit 2	1	Internal (osmotic)	Intratumoral	Histology
Shi *et al*., 2016[39]	Oxaliplatin	Liposomal	F98	Not mentioned for CED	30 µL/h	10 µL	20 min	1	33-gauge cannula	1	External	Intratumoral	Plasma mass spectrometry
Barth *et al*., 2016[40]	Cisplatin-containing EGFR-targeting bioconjugates	EGFR targeting	F98	Not mentioned for CED	20 µL/h	10 µL	30 min	1	Not mentioned	1	External	Intratumoral	No evaluation
Saucier-Sawyer *et al*., 2016[41]	PLGA BPNP	Nanoparticles	U87MG, RG2	Not mentioned	40 µL/h	20 µL	30 min	1	Stepped	1	External	Intratumoral	Histology
Yang *et al*., 2014[42]	Pegylated liposomal doxorubicin	Liposomal	F98	Not mentioned	Incremental: 12>30>48 µL/h	20 µL	(15/10/15) 40 min	1-4	Not mentioned	1	External	Intratumoral and peritumoral	Histology
Thisgaard *et al*., 2016[43]	Methotrexate ^{125}I-UdR	No coating	T87	No adverse effects observed	5 µL/h	1200 µL	10 days	1	PlasticsOne	1	Internal (iPRECIO infusion pump)	Intratumoral	SPECT/CT

EGFR – Epidermal growth factor receptor; BBB – Blood–brain barrier; RRV – Retroviral replicating vector; CED – Convection-enhanced delivery; SPECT – Single-photon emission computed tomography; CT – Computed tomography; EA – Ethylamine; PLGA BPNP – poly(lactic-co-glycolic acid) brain-penetrating nanoparticles; ICP-OES – inductively coupled plasma optical emission spectrometry

Table 3: Summary of clinical trial

Author and year	Agent infused	Type of drug	Type of tumor	Adverse effects	Flow rate	Total volume infused	Duration	Number of catheters	Cannula/ catheter	Number of infusions	Pump	Catheter placement	Evaluation of convection
Surapaneni *et al*., 2015[44]* Bruce *et al*., 2011[45]*	Topotecan	No coating	10 patients with GBM	No adverse effect	400 µL/h (2 catheters)	40,000 µL	100 h	1 or 2	Tunneled infusion catheters	1	External	Intratumoral	No evaluation

*Both publications used data generated from the same experiment. GBM – Glioblastoma

shown as areas with hypoattenuation. Of 30 studies, 9 (30%) studies used histology. Only 7/30 (23%) studies reported volume of distribution (Vd). Of 30 studies, 10 (33%) studies did not use a procedure to evaluate how the drug had been distributed.

Of 30 studies, 6 (20%) studies mentioned side effects due to the CED method. These were local edema and tissue damage along the cannula/catheter tract, gliosis, and necrosis. Side effects due to the different infused molecules were also mentioned but are not addressed in this review. Of 30 studies, 12 (40%) studies did not mention whether side effects due to the CED procedure occurred.

Discussion

The aim of this review was to provide an overview of the methodological aspects used in all preclinical and clinical studies published within the last 5 years where CED was used for drug delivery in the treatment of GBM. Based on this overview, we evaluated the catheter systems used, placement of catheters, infusion protocols applied, duration of infusions, number of infusions, the drugs infused, and how drug distribution was estimated.

The search resulted in 202 articles, of which 51 were duplicates. Of the remaining 151 studies, 64% were excluded (97 studies) because the studies were either nonexperimental or used another delivery method than CED. Among the remaining 54 studies, only 30 used GBM models. Altogether, only 30 studies focusing on CED for GBM therapy have been published over the course of the last 5 years. Since we only evaluated the methodological aspects of CED and not outcomes of survival or other outcome measures, one can argue that the risk of bias is low.

Of the 30 studies, only one study was a clinical study and the remaining 29 studies were conducted on rodents. This indicates that despite CED being known for over 20 years, it is still mainly used in preclinical studies. Moreover, we find it interesting that no data were generated in large brain animal models, despite the fact that successful translation of preclinical results depends on sufficient drug distribution in a large brain. Preclinically, this cannot be evaluated appropriately in small rodent models because it is far easier to obtain near whole-brain drug distribution in a small rodent brain compared to a larger nonrodent brain. The risk of overestimating the effect of a given convection-enhanced delivered drug is thus great if it has only been tested in a small rodent model. Moreover, the use of a large animal model will enable testing of the clinical CED system[46] in conjunction with the drug tested already in the preclinical phase. Unfortunately, only one large animal GBM model with human GBM cells has been described. This was an orthotopic GBM model in immunosuppressed pigs described by Selek *et al*.[47] They had a 93% tumor-take with the U87MG cell line but only 17% with a tumor stem cell line. In our opinion, future preclinical CED studies should, however, be a combination of small rodent studies and large animal nonrodent studies in tumor-bearing animals.

The technical aspects of the CED method deserve to be studied because optimizing the parameters of the CED method might also influence the results of preclinical drug development studies.

Of the 30 studies included in this review, only two studies done by Yang *et al*.[42] and Weng *et al*.[26] studied the technical aspects of the CED method.

Agent infused

In nearly all the 30 studies, different therapeutic agents were infused. The objective of most studies was to investigate the effect of drug coating with nanoparticles or liposomes to better control the release of a drug into the brain parenchyma or increase the area of drug distribution. Several studies investigated specific receptor targeting such as insulin-like growth factor receptor and epidermal growth factor receptor.[23,40] Only a few of the studies mentioned specific properties of the molecules they used, such as drug charge, hydrophilicity, or tissue affinity, although these properties influence the effective distribution of drugs in the brain by CED.[48]

Type of tumor

The type of tumor (i.e., the characteristics of the tissue in which the drug is to be distributed) is relevant to consider when applying the CED method.

A model should, as closely as possible, reflect the complexity of the human brain so that preclinical effect, toxicity, and safety can be determined before initiating a human clinical trial.

Twelve of the studies in this review have used the cell line U87-MG. Allen *et al*.[49] concluded that the origin of the widely used U87MG line is different from that of the original U87-MG from Uppsala.[49] Saucier-Sawyer *et al*.[41] described that their U87-MG cell line produces a tumor with circumscribed infiltration and limited necrosis,[41] making it a poor model of the human GBM tumor that is characterized by its extensive infiltration and necrosis. Eleven studies using U87-MG thus seem to have used a cell line that does not really mimic the properties of human GBM tumor tissue.

Catheter design

Seven studies used a stepped catheter for infusion. Of the remaining studies, nine used simple cannulas with sizes varying from 22-gauge to 33-gauge. Seven of the studies did not mention which type of cannula or catheter they used. It is surprising that such important information influencing CED was left out so often.

Most of the studies did not discuss their choice of catheter even though the design of the catheter plays an important

role in limiting the amount of backflow occurring along the catheter.[50] Several studies mention that catheters were slowly withdrawn or left in place for a short period after infusion. However, the effect on drug backflow using these procedures is not mentioned in the studies. The 32-gauge cannula, one of the smallest metal cannulas commercially available, must be used at a flow rate of 0.5 μl/min (30 μl/h) to avoid reflux,[50] a rate surpassed by many studies in this review.

A so-called step-design catheter has been proposed by Krauze *et al*.[51] It is a promising design that could enhance drug delivery by reducing both the infusion time and the volume of drug required to cover the targeted structure in the brain. Since the stepped catheters prevent reflux, they seem preferable compared to the often-used simple cannula or nonstepped designed catheters.[51]

From the wide array of catheters and cannulas used in the reviewed articles, one can only encourage that additional focus is given to catheter choice in future preclinical CED studies.

Catheter placement

The rationale behind peritumoral placement of catheters is to target the part of the GBM that is infiltrating healthy brain tissue. Yang *et al*.[42] investigated the effect of CED on four different experimental groups. The four groups were intratumoral infusion, peritumoral infusion after tumor removal, peritumoral infusion before tumor removal, and peritumoral infusion before tumor removal with prior use of steroids. They concluded that peritumoral infusion without prior tumor removal resulted in maximum Vd. The efficacy of the infusion was further enhanced by treatment with steroids before CED.[42] These are interesting findings, but in the clinical setting, the majority of GBM patients will have their tumor resected followed by adjuvant therapy. Moreover, the human brain is very large, and therefore, multiple catheters are probably needed.

Some articles mentioned that the tip of the catheter was placed at the center of the bulk tumor. However, the authors did not explain how this was achieved. It might be a difficult task when working with mice and rat brains because of their small size and without the help of a guiding system.

Flow rate and duration of infusion

In CED, the crucial aspect is to optimize flow by applying a pressure that forces penetration of the drug into the tissue. Although the precise mechanism is still not clear, interstitial fluid pressure is elevated in tumors.[52] This might be beneficial when treating highly invasive tumors, since the infused drug will spread further away from the bulk tumor. However, drug distribution inside the tumor mass might become compromised. It has been shown that the use of steroids before CED can reduce the interstitial pressure inside the tumor and can therefore reduce tumoral leakage.[42]

As seen in Tables 1-3, flow parameters vary between studies. It is unclear in most of the studies, why a particular flow rate or infusion time was chosen.

In the majority of studies, the infusion was kept at the same rate throughout the experiment. Interestingly, only five studies chose to use an incremental flow rate. Bobo *et al*.[4] used an incremental flow rate to increase the distribution of the infused agent. The logic behind using an incremental flow rate is to keep a constant positive pressure during the whole infusion period and avoid the pressure plateauing, ensuring that the infusion liquid penetrates the targeted area of tissue.[4]

Excessive flow pressure can, however, result in tissue fracturing, and once this occurs, the fracture will tend to propagate preventing the liquid from being properly distributed through the extracellular space.[50]

Schomberg *et al*.[53] concluded that ramping CED infusion protocols could potentially minimize backflow and produce more spherical infusion clouds, but further research is required to determine the strength of this correlation, especially in relation to maximum infusion rates.

Evaluation of drug distribution

One lesson learned from the only Phase III trial published to date (the PRECISE trial)[12] was that evaluation of drug distribution is crucial.[14] However, proper evaluation is not easily achieved.

In the reviewed articles, most studies used histology and only a few used computed tomography [CT] or MRI. However, eleven studies did not evaluate how their drugs were distributed at all. Although histological evaluation in preclinical studies might be relevant, it is not suitable for clinical use.

One method used for the evaluation of distribution is to coadminister a contrast agent with the drug and then presume that the distribution of the contrast agent, as shown on CT or MRI, equals that of the drug's distribution. However, from our own experience (unpublished data), this is not the case, which makes sense since a drug convects differently according to its size, charge, and tissue affinity.[48] Another method, used by the three studies in this review using MRI, was to conjugate iron oxide particles to the drug infused.[54] The distribution of the conjugates was then evaluated. A limitation of this approach is that conjugation (e.g., with iron oxide) alters the size and potentially the charge and tissue affinity.[55] Weng *et al*.[26] used a so-called quantum dot attached to a nanocarrier. The quantum dot emits an infrared light that can be measured with a charge-coupled device camera *ex vivo*. However, this technique only works on thin skulls such as mice.

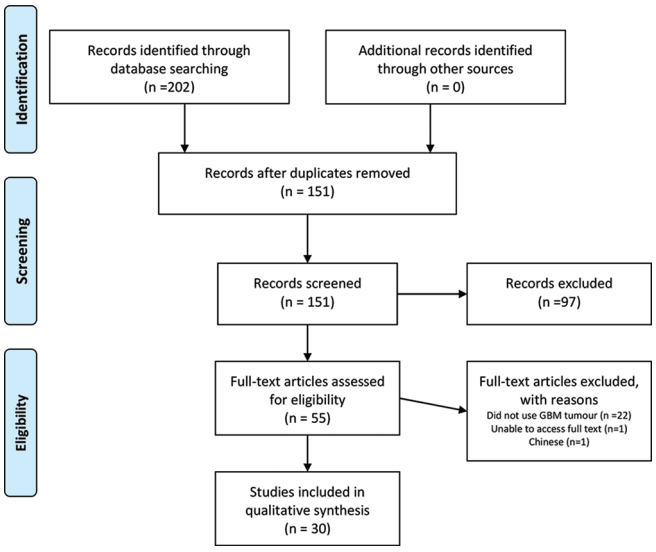

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram

In one of our own studies also included in this review, we infused a radiopharmaceutical (^{125}iodo-deoxyuridine).[43] This is a single photon emitter that can be visualized directly using single-photon emission CT imaging without any need for drug modification such as conjugation.

Conclusion

From 2011 to 2016, 30 studies have used CED for GBM therapy. Only one study was clinical, indicating that CED is still mostly explored preclinically. Since the first description of CED in 1994, it has become evident that the technical aspects of the infusion are important for the distribution of drugs and that there might be an important gain of therapeutic effect if good protocols can be developed.

This review shows that most researchers invested little interest in the methodological set-up of CED. This was true for catheter design, number of catheters used and their placement, infusion rate and start-up infusion protocol, and duration of infusion, indicating that the CED methodology was viewed as having only a small influence on the results of the drug studies. In general, the reporting on adverse effects was also severely lacking and even sometimes completely missing from the studies reviewed. It can also be added that endpoint measures are lacking in most of the studies: valid measures of the area of distribution of a given molecule with the given CED protocol using imaging such as MRI or CT combined with histology.

In our opinion, these aspects should be included in the future preclinical CED studies. Moreover, we find it crucial that the same CED protocols as those intended for use in humans are studied in large animals, such as tumor-bearing pigs, to overcome the challenges we face with translation of promising preclinical CED trials into successful clinical trials.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
2. Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA, *et al.* Maintenance therapy with tumor-treating fields plus temozolomide vs. temozolomide alone for glioblastoma: A Randomized Clinical Trial. JAMA 2015;314:2535-43.
3. Fakhoury M. Drug delivery approaches for the treatment of glioblastoma multiforme. Artif Cells Nanomed Biotechnol 2016;44:1365-73.
4. Bobo RH, Laske DW, Akbasak A, Morrison PF, Dedrick RL, Oldfield EH, *et al.* Convection-enhanced delivery of macromolecules in the brain. Proc Natl Acad Sci U S A 1994;91:2076-80.
5. Garland L, Gitlitz B, Ebbinghaus S, Pan H, de Haan H, Puri RK, *et al.* Phase I trial of intravenous IL-4 pseudomonas exotoxin protein (NBI-3001) in patients with advanced solid tumors that express the IL-4 receptor. J Immunother 2005;28:376-81.
6. Lidar Z, Mardor Y, Jonas T, Pfeffer R, Faibel M, Nass D, *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.
7. 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.
8. Weaver M, Laske DW. Transferrin receptor ligand-targeted toxin conjugate (Tf-CRM107) for therapy of malignant gliomas. J Neurooncol 2003;65:3-13.
9. Sampson JH, Akabani G, Archer GE, Bigner DD, Berger MS, Friedman AH, *et al.* Progress report of a Phase I study of the intracerebral microinfusion of a recombinant chimeric protein composed of transforming growth factor (TGF)-alpha and a mutated form of the pseudomonas exotoxin termed PE-38 (TP-38) for the treatment of malignant brain tumors. J Neurooncol 2003;65:27-35.
10. Weber F, Asher A, Bucholz R, Berger M, Prados M, Chang S, *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.
11. Allard E, Passirani C, Benoit JP. Convection-enhanced delivery of nanocarriers for the treatment of brain tumors. Biomaterials 2009;30:2302-18.
12. Kunwar S, Chang S, Westphal M, Vogelbaum M, Sampson J, Barnett G, *et al.* Phase III randomized trial of CED of IL13-PE38QQR vs. gliadel wafers for recurrent glioblastoma. Neuro Oncol 2010;12:871-81.
13. Kunwar S, Chang SM, Prados MD, Berger MS, Sampson JH, Croteau D, *et al.* Safety of intraparenchymal convection-enhanced delivery of cintredekin besudotox in early-phase studies. Neurosurg Focus 2006;20:E15.
14. Sampson JH, Archer G, Pedain C, Wembacher-Schröder E, Westphal M, Kunwar S, *et al.* Poor drug distribution as a possible explanation for the results of the PRECISE trial. J Neurosurg 2010;113:301-9.
15. Bouras A, Kaluzova M, Hadjipanayis CG. Radiosensitivity

enhancement of radioresistant glioblastoma by epidermal growth factor receptor antibody-conjugated iron-oxide nanoparticles. J Neurooncol 2015;124:13-22.
16. Kaluzova M, Bouras A, Machaidze R, Hadjipanayis CG. Targeted therapy of glioblastoma stem-like cells and tumor non-stem cells using cetuximab-conjugated iron-oxide nanoparticles. Oncotarget 2015;6:8788-806.
17. Wang W, Sivakumar W, Torres S, Jhaveri N, Vaikari VP, Gong A, *et al.* Effects of convection-enhanced delivery of bevacizumab on survival of glioma-bearing animals. Neurosurg Focus 2015;38:E8.
18. Danhier F, Messaoudi K, Lemaire L, Benoit JP, Lagarce F. Combined anti-galectin-1 and anti-EGFR siRNA-loaded chitosan-lipid nanocapsules decrease temozolomide resistance in glioblastoma: *In vivo* evaluation. Int J Pharm 2015;481:154-61.
19. Bernal GM, LaRiviere MJ, Mansour N, Pytel P, Cahill KE, Voce DJ, *et al.* Convection-enhanced delivery and *in vivo* imaging of polymeric nanoparticles for the treatment of malignant glioma. Nanomedicine 2014;10:149-57.
20. Chen PY, Ozawa T, Drummond DC, Kalra A, Fitzgerald JB, Kirpotin DB, *et al.* Comparing routes of delivery for nanoliposomal irinotecan shows superior anti-tumor activity of local administration in treating intracranial glioblastoma xenografts. Neuro Oncol 2013;15:189-97.
21. Sonabend AM, Carminucci AS, Amendolara B, Bansal M, Leung R, Lei L, *et al.* Convection-enhanced delivery of etoposide is effective against murine proneural glioblastoma. Neuro Oncol 2014;16:1210-9.
22. Stephen ZR, Kievit FM, Veiseh O, Chiarelli PA, Fang C, Wang K, *et al.* Redox-responsive magnetic nanoparticle for targeted convection-enhanced delivery of O6-benzylguanine to brain tumors. ACS Nano 2014;8:10383-95.
23. Zamykal M, Martens T, Matschke J, Günther HS, Kathagen A, Schulte A, *et al.* Inhibition of intracerebral glioblastoma growth by targeting the insulin-like growth factor 1 receptor involves different context-dependent mechanisms. Neuro Oncol 2015;17:1076-85.
24. Suzuki A, Leland P, Kobayashi H, Choyke PL, Jagoda EM, Inoue T, *et al.* Analysis of biodistribution of intracranially infused radiolabeled interleukin-13 receptor-targeted immunotoxin IL-13PE by SPECT/CT in an orthotopic mouse model of human glioma. J Nucl Med 2014;55:1323-9.
25. Shultz MD, Wilson JD, Fuller CE, Zhang J, Dorn HC, Fatouros PP, *et al.* Metallofullerene-based nanoplatform for brain tumor brachytherapy and longitudinal imaging in a murine orthotopic xenograft model. Radiology 2011;261:136-43.
26. Weng KC, Hashizume R, Noble CO, Serwer LP, Drummond DC, Kirpotin DB, *et al.* Convection-enhanced delivery of targeted quantum dot-immunoliposome hybrid nanoparticles to intracranial brain tumor models. Nanomedicine (Lond) 2013;8:1913-25.
27. Halle B, Marcusson EG, Aaberg-Jessen C, Jensen SS, Meyer M, Schulz MK, *et al.* Convection-enhanced delivery of an anti-miR is well-tolerated, preserves anti-miR stability and causes efficient target de-repression: A proof of concept. J Neurooncol 2016;126:47-55.
28. Mendiburu-Eliçabe M, Gil-Ranedo J. Combination therapy of intraperitoneal rapamycin and convection- enhanced delivery of nanoliposomal CPT-11 in rodent orthotopic brain tumor xenografts. Curr Cancer Drug Targets 2015;15:352-62.
29. Cooper I, Last D, Guez D, Sharabi S, Elhaik Goldman S, Lubitz I, *et al.* Combined local blood-brain barrier opening and systemic methotrexate for the treatment of brain tumors. J Cereb Blood Flow Metab 2015;35:967-76.
30. Yang W, Barth RF, Huo T, Nakkula RJ, Weldon M, Gupta N, *et al.* Radiation therapy combined with intracerebral administration of carboplatin for the treatment of brain tumors. Radiat Oncol 2014;9:25.
31. Xi G, Robinson E, Mania-Farnell B, Vanin EF, Shim KW, Takao T, *et al.* Convection-enhanced delivery of nanodiamond drug delivery platforms for intracranial tumor treatment. Nanomedicine 2014;10:381-91.
32. Yin D, Zhai Y, Gruber HE, Ibanez CE, Robbins JM, Kells AP, *et al.* Convection-enhanced delivery improves distribution and efficacy of tumor-selective retroviral replicating vectors in a rodent brain tumor model. Cancer Gene Ther 2013;20:336-41.
33. Huo T, Barth RF, Yang W, Nakkula RJ, Koynova R, Tenchov B, *et al.* Preparation, biodistribution and neurotoxicity of liposomal cisplatin following convection enhanced delivery in normal and F98 glioma bearing rats. PLoS One 2012;7:e48752.
34. Phillips WT, Goins B, Bao A, Vargas D, Guttierez JE, Trevino A, *et al.* Rhenium-186 liposomes as convection-enhanced nanoparticle brachytherapy for treatment of glioblastoma. Neuro Oncol 2012;14:416-25.
35. Xi G, Rajaram V, Mania-Farnell B, Mayanil CS, Soares MB, Tomita T, *et al.* Efficacy of vincristine administered via convection-enhanced delivery in a rodent brainstem tumor model documented by bioluminescence imaging. Childs Nerv Syst 2012;28:565-74.
36. Shi M, Fortin D, Sanche L, Paquette B. Convection-enhancement delivery of platinum-based drugs and lipoplatin (TM) to optimize the concomitant effect with radiotherapy in F98 glioma rat model. Invest New Drugs 2015;33:555-63.
37. Zhang R, Saito R, Mano Y, Sumiyoshi A, Kanamori M, Sonoda Y, *et al.* Convection-enhanced delivery of SN-38-loaded polymeric micelles (NK012) enables consistent distribution of SN-38 and is effective against rodent intracranial brain tumor models. Drug Deliv 2016;23:2780-6.
38. Hiramatsu R, Kawabata S, Tanaka H, Sakurai Y, Suzuki M, Ono K, *et al*. Tetrakis (p-carboranylthio-tetrafluorophenyl) Chlorin (TPFC): Application for photodynamic therapy and boron neutron capture therapy. J Pharm Sci 2015;104:962-70.
39. Shi M, Fortin D, Paquette B, Sanche L. Convection-enhancement delivery of liposomal formulation of oxaliplatin shows less toxicity than oxaliplatin yet maintains a similar median survival time in F98 glioma-bearing rat model. Invest New Drugs 2016;34:269-76.
40. Barth RF, Wu G, Meisen WH, Nakkula RJ, Yang W, Huo T, *et al.* Design, synthesis, and evaluation of cisplatin-containing EGFR targeting bioconjugates as potential therapeutic agents for brain tumors. Onco Targets Ther 2016;9:2769-81.
41. Saucier-Sawyer JK, Seo YE, Gaudin A, Quijano E, Song E, Sawyer AJ, *et al.* Distribution of polymer nanoparticles by convection-enhanced delivery to brain tumors. J Control Release 2016;232:103-12.
42. Yang X, Saito R, Nakamura T, Zhang R, Sonoda Y, Kumabe T, *et al.* Peri-tumoral leakage during intra-tumoral convection-enhanced delivery has implications for efficacy of peri-tumoral infusion before removal of tumor. Drug Deliv 2016;23:781-6.
43. Thisgaard H, Halle B, Aaberg-Jessen C, Olsen BB, Therkelsen AS, Dam JH, *et al.* Highly effective auger-electron therapy in an orthotopic glioblastoma xenograft model using convection-enhanced delivery. Theranostics 2016;6:2278-91.
44. Surapaneni K, Kennedy BC, Yanagihara TK, DeLaPaz R, Bruce JN. Early cerebral blood volume changes predict progression after convection-enhanced delivery of topotecan for recurrent malignant glioma. World Neurosurg 2015;84:163-72.

45. Bruce JN, Fine RL, Canoll P, Yun J, Kennedy BC, Rosenfeld SS, *et al.* Regression of recurrent malignant gliomas with convection-enhanced delivery of topotecan. Neurosurgery 2011;69:1272-9.
46. Barua NU, Woolley M, Bienemann AS, Johnson DE, Lewis O, Wyatt MJ, *et al.* Intermittent convection-enhanced delivery to the brain through a novel transcutaneous bone-anchored port. J Neurosci Methods 2013;214:223-232.
47. Selek L, Seigneuret E, Nugue G, Wion D, Nissou MF, Salon C, *et al.* Imaging and histological characterization of a human brain xenograft in pig: The first induced glioma model in a large animal. J Neurosci Methods 2014;221:159-65.
48. Barua NU, Gill SS, Love S. Convection-enhanced drug delivery to the brain: Therapeutic potential and neuropathological considerations. Brain Pathol 2014;24:117-27.
49. Allen M, Bjerke M, Edlund H, Nelander S, Westermark B. Origin of the U87MG glioma cell line: Good news and bad news. Sci Transl Med 2016;8:1-4.
50. White E, Bienemann A, Malone J, Megraw L, Bunnun C, Wyatt M, *et al.* An evaluation of the relationships between catheter design and tissue mechanics in achieving high-flow convection-enhanced delivery. J Neurosci Methods 2011;199:87-97.
51. Krauze MT, Saito R, Noble C, Tamas M, Bringas J, Park JW, *et al.* Reflux-free cannula for convection-enhanced high-speed delivery of therapeutic agents. J Neurosurg 2005;103:923-9.
52. Boucher Y, Baxter LT, Jain RK. Interstitial pressure gradients in tissue-isolated and subcutaneous tumors: Implications for therapy. Cancer Res 1990;50:4478-84.
53. Schomberg D, Wang A, Marshall H, Miranpuri G, Sillay K. Ramped-rate vs. continuous-rate infusions: An *in vitro* comparison of convection enhanced delivery protocols. Ann Neurosci 2013;20:59-64.
54. Hadjipanayis CG, Machaidze R, Kaluzova M, Wang L, Schuette AJ, Chen H, *et al.* EGFRvIII antibody-conjugated iron oxide nanoparticles for magnetic resonance imaging-guided convection-enhanced delivery and targeted therapy of glioblastoma. Cancer Res 2010;70:6303-12.
55. Zhou J, Atsina KB, Himes BT, Strohbehn GW, Saltzman WM. Novel delivery strategies for glioblastoma. Cancer J 2012;18:89-99.