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Clinical Study

First in human nanotechnology doxorubicin delivery system to target epidermal growth factor receptors in recurrent glioblastoma

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ABSTRACT

There are limited treatment options for patients with recurrent glioblastoma (GBM). The EnGeneIC delivery vehicle (EDV) is a novel nanocellular (minicell) compound which packages theoretically effective concentrations of chemotherapeutic drugs that are designed to target tumors via minicell-surface attached bispecific proteins (EnGeneIC, Lane Cove West, NSW, Australia). Epidermal growth factor receptor (EGFR) is overexpressed in 40–50% of patients with GBM and is a promising target for new therapeutics. $^{V}EDV_{Dox}$ contains doxorubicin (Dox) within the minicells and targets EGFR through Vectibix (V; Amgen Biologicals, Thousand Oaks, CA, USA). We conducted a first in human Phase I study of $^{V}EDV_{Dox}$ in adults with recurrent GBM expressing EGFR on immunohistochemistry, following standard therapy including radiation and temozolomide, to establish a safe maximum tolerated dose and determine a recommended Phase II dose (RPTD). $^{V}EDV_{Dox}$ was administered weekly in an 8 week cycle, with dose escalation in successive cohorts of patients using a standard 3 + 3 design. In total, 14 patients were treated at three dose levels, and the RPTD was identified as 5×10^9 $^{V}EDV_{Dox}$. Overall $^{V}EDV_{Dox}$ was well tolerated, with no dose limiting toxicity and no withdrawals from the study due to adverse events. The most common adverse events were nausea, fever, and chills or rigors, experienced in seven, five and five patients, respectively. Transient uncomplicated hypophosphatemia was seen in seven patients and was not dose-related. Our results demonstrate that $^{V}EDV_{Dox}$, up to a dose of 5×10^9 $^{V}EDV_{Dox}$ weekly, is well tolerated in patients with recurrent GBM.

1. Introduction

Glioblastoma (GBM) is the most aggressive glial tumor, accounting for 60–70% of malignant gliomas [1]. Disease recurrence or progression is almost inevitable for patients with GBM, despite a multimodality approach using surgery, radiotherapy and temozolomide chemotherapy. For patients whose tumors recur, the median time to progression is less than 6 months [2], highlighting the need to develop new therapeutic strategies. Bevacizumab has efficacy in recurrent GBM, but the median progression free (PFS) and overall survival (OS) for patients with recurrent disease in a non-comparative Phase II trial was 4.2 and 9.2 months, respectively [3].

The EnGeneIC delivery vehicle (EDV; EnGeneIC, Lane Cove West, NSW, Australia; Fig. 1) is a novel compound that can package theoretically effective concentrations of chemotherapeutic drugs into minicells (400 nm nanoparticles derived from *Salmonella typhimurium*) which are then targeted to tumors via minicell-surface attached bispecific antibodies [4]. In this study of $^{V}EDV_{Dox}$, we packaged doxorubicin (Dox) and used panitumumab/Vectibix (V; Amgen Biologicals, Thousand Oaks, CA, USA) to target the epidermal growth factor receptor (EGFR) protein on the tumor cell. Upon binding to EGFR, it was anticipated that $^{V}EDV_{Dox}$ would be internalized and doxorubicin released intracellularly. Based on preclinical studies, it was identified that $^{V}EDV_{Dox}$ contains a mean of 500 ng (± a standard deviation of 100) of doxorubicin and <5 μg of anti-human EGFR (Vectibix sequence) per 10^9 EDV.

The choice of EGFR as the target, and the use of Vectibix as the antibody, was based on the knowledge that EGFR appears to play a

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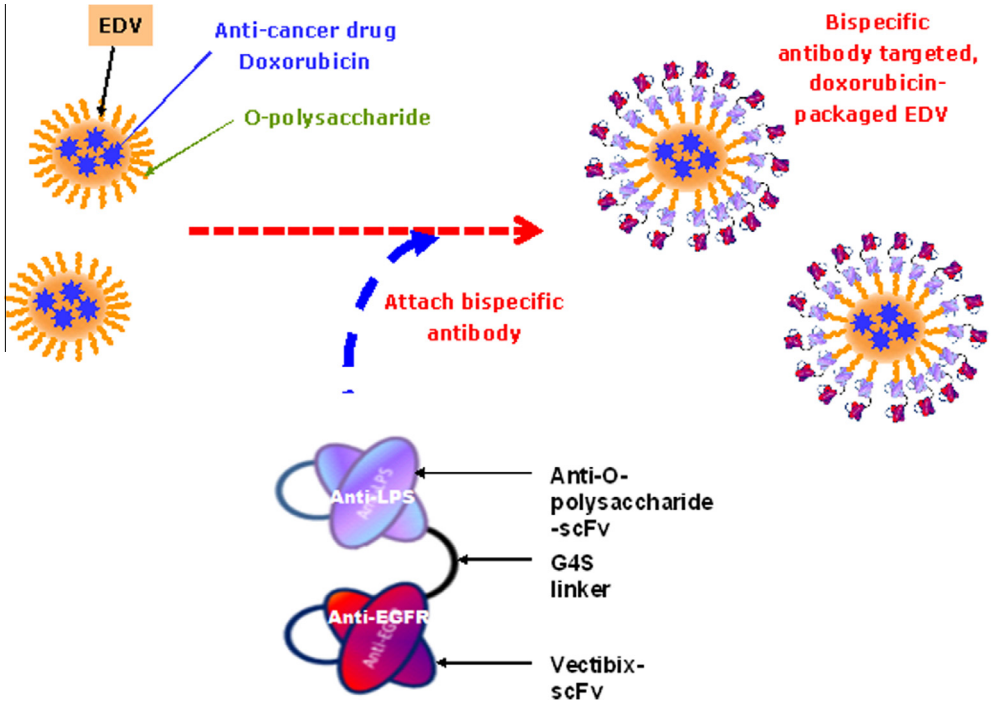

Fig. 1. The three component delivery system of the EnGeneIC delivery vehicle (EDV; EnGeneIC, Lane Cove West, NSW, Australia) with doxorubicin and Vectibix (Amgen Biologicals, Thousand Oaks, CA, USA). EGFR = epithelial growth factor receptor, LPS = lipopolysaccharide, scFv = single chain variable fragment.

critical role in GBM [5,6]. EGFR is amplified and overexpressed in 40–50% of GBM [7], and is an obvious target for novel therapies. However, the efficacy of small molecule EGFR inhibitors (erlotinib and gefitinib) or monoclonal antibodies (cetuximab) in the treatment of GBM has been disappointing [8,9]. The choice of doxorubicin as the packaged chemotherapy was based on *in vitro* [10–12] and *in vivo* studies which have shown that doxorubicin is active in a variety of glioma models, particularly when using novel delivery systems [13]. In addition, liposomal doxorubicin has efficacy in the setting of recurrent GBM [14–19]. Furthermore, anthracycline analogues such as MX-2, a morpholino anthracycline, were shown to have moderate activity in recurrent GBM [20]. Finally, the use of EDV with Dox and anti-EGFR antibody ($^{\text{Anti-EGFR}}\text{EDV}_{\text{Dox}}$) in dogs with primary brain tumors has demonstrated efficacy (J.A.M. and H.B, unpublished data).

We have previously conducted a first in human study of EDV with the anti-human EGFR Erbitux (ImClone, Indianapolis, IN, USA) and paclitaxel ($^{\text{Erbitux}}\text{EDV}_{\text{Paclitaxel}}$), and established a recommended Phase II dose (RPTD) of 5×10^{9} $^{\text{Erbitux}}\text{EDV}_{\text{Paclitaxel}}$, as well as identifying the dose limiting toxicity (DLT) of Grade 4 elevation in aspartate transaminase and alanine transaminase [21]. Other notable toxicities included transient hypophosphatemia, as well as fevers associated with elevation in cytokines and inflammatory markers such as interleukin 6 (IL-6). The current trial represents a first in class study of an EDV monotherapy for recurrent GBM. The primary objective for the dose exploration study was aimed at determining the maximum tolerated dose (MTD) and RPTD.

2. Materials and methods

2.1. Patient eligibility

The eligible patients were adults with histologically confirmed recurrent or progressive GBM that expressed EGFR and had measurable disease on MRI. A baseline MRI was performed within 14 days of the study enrollment, while on a stable dose of steroid medication for $\geqslant$5 days. An interval of $\geqslant$4 weeks from surgical resection, and $\geqslant$12 weeks from the completion of radiotherapy, was required prior to study entry. The patients may have received one additional chemotherapy agent other than temozolomide, and completion of treatment was more than 4 weeks prior to study entry. They must have recovered from all toxic effects prior to registration, and prior bevacizumab or other anti-angiogenic therapy was not permitted.

The eligible patients had Eastern Cooperative Oncology Group (ECOG) performance statuses of 0–2. They were required to have adequate bone marrow, renal, hepatic, and cardiac function. Anti-coagulation therapy, except low molecular weight heparins or low dose aspirin, was not permitted. All patients with reproductive potential must have been using appropriate and effective contraception. The exclusion criteria included: previous or current malignancy at another site (except adequately treated non-melanoma skin cancer, curatively treated *in situ* cancer, or other solid tumors curatively treated with no evidence of disease for $\geqslant$2 years), history of central nervous system bleeding, unstable cardiac disease, active infection, pregnancy or breast feeding, or any other disorder that would hamper compliance with the study and follow-up.

The study design was approved by the Institutional Review Boards at all participating institutions prior to patient enrollment, and the patients were required to give written informed consent.

2.2. Treatment design and dose escalation

This was an open label, multicenter, Phase I/II clinical study of the single agent $^{\text{V}}\text{EDV}_{\text{Dox}}$, administered intravenously (IV) over 20 minutes, once weekly, in patients with recurrent GBM expressing EGFR. $^{\text{V}}\text{EDV}_{\text{Dox}}$ was supplied by EnGeneIC. One treatment cycle consisted of eight infusions of $^{\text{V}}\text{EDV}_{\text{Dox}}$. Premedication consisted of 8 mg IV dexamethasone, 1 g oral paracetamol and 12.5–25 mg IV or 25 mg oral promethazine. The premedication schedule was determined based on the Phase I study [21], and the occurrence of self-limiting fevers and chills in 57 and 53% of patients,

respectively. The treatment continued until disease progression, unacceptable toxicity or withdrawal for other reasons.

The study used a standard 3 + 3 dose escalation design to evaluate three dose strata: 1×10^9 $^{V}EDV_{Dox}$ (Level 1), 2×10^9 $^{V}EDV_{Dox}$ (Level 1), 5×10^9 $^{V}EDV_{Dox}$ (Level 2), and 8×10^9 $^{V}EDV_{Dox}$ (Level 3). There were three patients entered at each dose stratum, and this was expanded to six patients per dose stratum if a DLT was seen in the first three patients. The aim was to establish the RPTD of $^{V}EDV_{Dox}$. Three patients would complete 4 weeks of treatment to ensure safety and then dose escalation would occur, or additional patients would be added to that dose level if any DLT was observed.

The MTD was defined as the dose where two or more DLT were seen. The RPTD was defined as the dose below the MTD or, if an MTD was not determined, the highest dose level tested. All toxicities or adverse events were graded according to the common terminology criteria for adverse events (CTCAE) (version 4). A DLT was defined as a toxicity or adverse event occurring within the first 28 days, attributable to the study treatment and meeting one of the following criteria: any clinically significant Grade 3/4 non-hematological toxicity with the exclusion of nausea and vomiting, fever, asymptomatic hyperglycemia, asymptomatic hyperuricemia, biochemical abnormalities that resolved to Grade 2 or better in $\leqslant$7 days; febrile neutropenia, defined as absolute neutrophil count $<1.0 \times 10^9$/L and fever $\geqslant$38.5°C; Grade 4 neutropenia for $\geqslant$7 days; Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia for $\geqslant$7 days.

The study was designed to include an expansion cohort at the RPTD of up to 46 patients with recurrent GBM. The second part of the study was to confirm the safety and tolerability of $^{V}EDV_{Dox}$ and to evaluate efficacy. The study sponsor (EnGeneIC Inc.) closed the study at the completion of the dose escalation phase so that the dose expansion did not take place.

2.3. Dose modification

The resumption of treatment after resolution of a DLT was permitted, if clinically appropriate, contingent on a return of the DLT to $\leqslant$ Grade 1 severity and that the interruption or delay of treatment was no more than 3 weeks. The resumption of treatment was at the next lower dose level (or 50% lower if the DLT occurred with the first dose level). The patients who required more than 3 weeks of recovery from clinically significant unrelated Grade $\geqslant$ 3 toxicities were withdrawn from the study.

2.4. Patient evaluation

A performance status evaluation, clinical examination, 12-lead electrocardiogram (ECG), and neurological evaluation were performed before days 1, 8 and 29 of each cycle. An hematological assessment, clinical chemistry tests, blood sampling for immune/inflammatory response analyses, and antibodies to *Salmonella* and anti-EGFR were performed weekly for cycle 1, and then three times weekly from cycle 2 onwards. The tumor response was evaluated by contrast enhanced MRI, performed at screening, after week 8 of treatment (one cycle), and then every 8 weeks thereafter, using the response assessment in neuro-oncology (RANO) criteria [22]. The patients with a demonstrated objective response (complete [CR] or partial response [PR]) were required to have a confirmatory MRI no less than 4 weeks after the last scan. The treating physician's assessment of the RANO response was used to make all study treatment decisions.

2.5. Endpoints

The dose escalation component of the study was aimed at determining the MTD in this patient cohort and identifying the RPTD. Following dose exploration, the dose expansion phase was to be completed with a primary endpoint of 6 months of progression free survival (PFS-6), according to the RANO criteria in recurrent GBM. The secondary endpoints were objective tumor response according to RANO criteria, PFS, OS, assessment of safety and tolerability of $^{V}EDV_{Dox}$, and to estimate the time to response and duration of response. Other exploratory analyses included an assessment of immune and cytokine responses in patients receiving $^{V}EDV_{Dox}$, and to investigate potential biomarker development.

2.6. EGFR immunohistochemistry

EGFR protein expression was assessed by immunohistochemistry using the EGFR PharmDx kits (Dako, Glostrup, Denmark). Stained slides were reviewed by a pathologist, and tumors with more than 20% of tumor cells demonstrating membranous (partial or complete) staining of any intensity, were considered positive.

2.7. Pharmacokinetic and biological endpoint evaluation

For cycle 1, before the dose and at 3 and 24 hours, blood samples were obtained for pharmacokinetic (PK) analysis. Plasma from these blood samples was evaluated for estimation of $^{V}EDV_{Dox}$ concentration. Cytokine and interferon responses were also evaluated.

2.8. Statistical analyses

The patients who received at least one cycle of treatment were eligible for response evaluation. The primary response variable was PFS-6. The sample size was based on the minimax design proposed by Simon et al. [23] for a two stage dose expansion study. The following set of parameters were selected by taking into consideration that historically, chemotherapy for recurrent GBM has a 15% PFS-6, while bevacizumab has a 35% PFS-6: $P_0 = 0.20$, $P_1 = 0.4$, alpha = 0.05, beta = 0.20.

These choices of parameters lead to the following sample sizes: 18 patients were to be enrolled in the first stage, and the trial would be stopped if four or less patients were progression free at 6 months. Otherwise, the trial would continue in part two until a total of 46 patients were enrolled.

Demographic and baseline characteristics were recorded as medians (with ranges) for continuous variables and proportions for categorical variables.

3. Results

3.1. Patient characteristics

Between 5 February 2013 and 6 June 2014, 14 patients in three dose strata were treated in 8 week cycles, three at Level 1 (2×10^9 $^{V}EDV_{Dox}$), three at Level 2 (5×10^9 $^{V}EDV_{Dox}$) and eight at Level 3 (8×10^9 $^{V}EDV_{Dox}$).

Six patients failed to complete one treatment cycle due to progressive disease. In total, three patients completed at least four cycles of treatment. The patient characteristics are shown in Table 1. Six patients (43%) were enrolled at their first recurrence, seven patients (50%) at their second recurrence and one patient (7%) at the time of their third GBM recurrence. All tumors expressed EGFR.

3.2. Safety and tolerability

No patient experienced a DLT, no patient withdrew from the study due to an adverse event and no treatment-related deaths occurred. Table 2 summarizes the toxicities that did not meet

Table 1
Patient characteristics

Characteristic	n (%)
Age, median years (range)	55 (35–71)
Male sex	7 (50)
ECOG	
0	6 (43)
1	7 (50)
2	1 (7)
Chemotherapy regimens before enrollment	
1	12 (86)
2	2 (14)

ECOG = Eastern Cooperative Oncology Group performance status.

DLT criteria. A total of 21 complete 8 week cycles of $^{V}EDV_{Dox}$ were administered in eight patients.

The MTD was not reached. A decision was made by the investigators that further dose escalation was unlikely to be of value, given the previous Phase I study [21] and the toxicity that was seen at higher doses. As a consequence, dose Level 3 was considered appropriate as the RPTD, and dose expansion would occur at this dose level. The study was ceased at the request of the sponsor with eight patients treated at dose Level 3.

Overall, $^{V}EDV_{Dox}$ was well tolerated. The most common toxicities were nausea, fever, and chills or rigors, experienced by seven, five, and five patients, respectively. The majority of patients experienced a mild self-limiting rise in white blood cells and neutrophils at 3–24 hours post dose, which returned to baseline prior to each subsequent treatment. Other hematological parameters were not affected by $^{V}EDV_{Dox}$. Two patients in dose Level 1 and two patients in dose Level 3 experienced Grade 3 hypophosphatemia attributed to the study drug, which was uncomplicated and asymptomatic.

During the course of the study, six patients experienced serious adverse events. Of these, two were considered to be related to the study treatment and required hospitalization. One patient experienced muscular weakness and pyrexia, approximately 12 hours after the first dose, which resulted in hospitalization. The second dose was similar to the first and the patient was admitted overnight. This patient was positive for *S. typhimurium* antibodies at screening, but had a negative titer prior to administration of dose 1. A second patient experienced hypotension 3 hours post infusion, which required IV hydration and hospitalization. This patient was admitted overnight and an assessment of their urine indicated an *Escherichia coli* urinary tract infection for which the patient was treated. This was not considered a DLT as it was directly attributable to the urinary tract infection.

3.3. Inflammatory markers

Excluding one patient with elevated levels of cytokines at study entry, all other patients showed transient increases in interleukins, IL-6, IL-8 and IL-10, at 3 hours following the first dose of the drug, and all had returned to baseline by the 24 hour post dose measurement. This response was also observed in cycles 2 and 3. All other cytokines were within the normal reference ranges, and there was no clear dose response evident within these measurements.

3.4. S. typhimurium antibodies

Antibodies to *S. typhimurium* (anti-lipopolysaccharide immunoglobulin G) were assessed at screening. Thirteen of 14 patients (93%) were negative for *S. typhimurium* antibodies at screening. One patient assigned to dose Level 2 was positive at screening. All patients who were initially negative for *S. typhimurium* antibodies showed an initial rise in antibody titer through to dose 3. The overall increase in titer ranged from four-fold to 30-fold, compared with pretreatment levels with a mean of 14-fold). Four patients developed positive *S. typhimurium* antibody titers after a single dose, with the remainder of the cohort developing positive titers following administration of the second dose. The titers were maintained with no further augmentation over subsequent doses, despite one patient receiving a total of 47 doses.

3.5. Pharmacokinetic and biological endpoints

PK analysis was not performed as the Dox levels were too low to be detected. In addition, anti-EGFR antibody analysis was only to be performed in the dose expansion phase, therefore, this was also not performed.

Table 2
Toxicity

Toxicity grade	Grades 1–2				Grades 3–4			
$^{V}EDVs_{Dox}$[a] dose level	Level 1[b], n	Level 2[c], n	Level 3[d], n	All, n (%)	Level 1[b], n	Level 2[c], n	Level 3[d], n	All, n (%)
Patients	3	3	8	14	3	3	8	14
Complications				14 (100)				6 (43)
Investigation								
Lymphopenia	0	0	0	0 (0)	1	0	0	1 (7)
ALT increased	0	0	0	0 (0)	0	0	1	1 (7)
AST increased	0	0	0	0 (0)	0	0	1	1 (7)
Hypophosphatemia	0	3	0	3 (21)	2	0	2	4 (29)
Clinical								
Fever	1	1	3	5 (36)	0	0	0	0
Chills/rigor	1	2	2	5 (36)	0	0	0	0
Nausea/emesis	1	2	4	7 (50)	0	0	0	0
Headache	1	1	2	4 (29)	0	0	0	0
Muscular weakness	0	1	2	3 (21)	0	1	0	1 (7)
Hypotension	0	0	0	0 (0)	0	0	1	1 (7)

[a] EnGeneIC, Lane Cove West, NSW, Australia.
[b] Level 1 = 2×10^9 $^{V}EDVs_{Dox}$.
[c] Level 2 = 5×10^9 $^{V}EDVs_{Dox}$.
[d] Level 3 = 8×10^9 $^{V}EDVs_{Dox}$.
ALT = alanine transaminase, AST = aspartate transaminase, $^{V}EDVs_{Dox}$ = EnGeneIC delivery vehicle (EDV) with doxorubicin (Dox) and Vectibix (V; Amgen Biologicals, Thousand Oaks, CA, USA).

Table 3
Efficacy outcomes

Population	n	OS, median months (range)[a]	PFS, median months (range)	PFS-6, n (%)
Level 1 (2×10^9 $^{V}EDVs_{Dox}$)[b]	3	12.3 (9.3–23.6)	1.8 (0.8–7.2)	1 (33)
Level 2 (5×10^9 $^{V}EDVs_{Dox}$)[b]	3	9.1 (4.3–10.1)	5.4 (0.8–7.2)	0 (0)
Level 3 (8×10^9 $^{V}EDVs_{Dox}$)[b]	8	12.6 (2.1–20)	1.4 (0.7–11.3)	1 (13)
Total	14	9.7 (2.1–23.6)	1.6 (0.7–11.3)	2 (14)

[a] Overall survival as at 1 February 2015.
[b] EnGeneIC, Lane Cove West, NSW, Australia.
OS = overall survival, PFS = progression free survival, PFS-6 = 6 months of progression free survival, $^{V}EDVs_{Dox}$ = EnGeneIC delivery vehicle (EDV) with doxorubicin (Dox) and Vectibix (V; Amgen Biologicals, Thousand Oaks, CA, USA).

3.6. Outcome and anti-tumor response

All 14 patients were evaluated for response, of whom, eight completed one cycle (eight doses). Four patients completed more than one cycle. The median PFS for all patients was 1.6 months (range: 0.6–11). Two patients (14%) had a PFS of greater than 6 months (Table 3). The median OS was 9 months and 21 days (range: 2–23.6). Three patients who completed at least one cycle were alive at 1 February 2015, with survival times of $\geqslant$24, 20, and 19 months from the first dose of $^{V}EDV_{Dox}$. No patients achieved a PR or CR according to the RANO criteria. The best response observed was stable disease in four patients (28%). One patient in Level 1, one in Level 2 and one in Level 3 had stable disease after cycle 3. One patient had stable disease after cycle 6.

4. Discussion

For patients with recurrent GBM following radiation and temozolomide, there is no current standard of care and the overall prognosis is poor. The current options include further surgery, second line chemotherapy and stereotactic radiosurgery [24]. Therefore, there is a clear need to identify novel therapeutic approaches to improve outcomes [25]. EGFR is overexpressed in 40–50% of GBM [7] and is an attractive target for new drug development. Despite the preclinical rationale, treatment with the EGFR tyrosine kinase inhibitors gefitinib and erlotinib has been disappointing [8,26].

The EDV is a novel and innovative nanocellular technology with the potential to safely and effectively treat patients with a number of solid organ malignancies. In the present study, we report on the Phase I results of $^{V}EDV_{Dox}$ in patients with recurrent GBM. We utilized the anti-EGFR monoclonal antibody Vectibix to target the EGFR protein on cancer cells and allow internalization of the construct, with the subsequent release of Dox. This study represents the first in class trial of an EDV administered as monotherapy for recurrent GBM.

The preclinical assessment of the EDV demonstrated that a high concentration of up to one million drug molecules can be packaged within a minicell [27]. In mouse xenograft studies, tumor regression was demonstrated in breast, lung, ovarian and colon cancer, with no signs of toxicity. The potency observed in the xenograft models may depend on the concentration of a drug that is delivered intracellularly within cancer cells [27]. Interestingly, potent antitumor effects could be seen at 1875 and 8000-fold lower amounts of docetaxel and paclitaxel, respectively, delivered to xenografts via minicells, compared to the respective free drugs [27]. Biodistribution studies in tumor bearing mice demonstrated that approximately 30% of the injected dose of Dox was found in tumors, as demonstrated by iodine isotope 125 (^{125}I)-labeled minicells. Furthermore, biodistribution studies in two dogs using $^{Anti\text{-}EGFR}EDV$ radio-labeled with ^{123}I demonstrated the expected uptake in the liver, as well as in the brain tumor itself (J.A.M. and H.B., unpublished data).

The data reported here, from 14 patients who were treated with $^{V}EDV_{Dox}$ at three dose levels, identified a MTD of 5×10 $^{V}EDV_{Dox}$. The trial was terminated by the sponsor prior to recruitment of all 18 patients, who were required to establish part 1 of the Simon two step strategy in evaluating efficacy. As a consequence, the key efficacy parameters have not been achieved and we cannot definitively establish whether $^{V}EDV_{Dox}$ has significant clinical efficacy. Therefore, the interpretation of any response must be reviewed with caution. The median PFS for all patients was 1.6 months (range: 0.6–11) and two patients (14%) had a PFS >6 months. No patients achieved a PR or CR according to the RANO criteria. Four patients (28%) had stable disease. The median OS for all patients was 9 months and 21 days (range: 2–23.6).

At the dose levels used, therapy with $^{V}EDV_{Dox}$ is well tolerated with manageable side effects. This was similar to the results of the first time in human study of $^{Erbitux}EDV_{Paclitaxel}$, where we identified transient hypophosphatemia, as well as fevers, associated with an elevation of cytokines and inflammatory markers such as IL-6 [21]. Here, we also report transient hypophosphatemia and fever which was not dose-dependent. The inflammatory responses may be attributable to the bacterial cell of origin for the minicells, with the knowledge that bacterial products can induce inflammatory responses activated by Toll-like receptors.

This study has a number of limitations, particularly due to its early closure, but also due to some biological issues. First, despite EGFR representing a clear target for GBM, multiple clinical trials with EGFR inhibitors [8,9] have been disappointing. The molecular basis for these disappointing results remains unclear, although it may include inactivation of a conformational change, extracellular domain mutations, as well as interactions between wild-type and mutant EGFR [28,29]. These potential issues may be less important for the proposed drug delivery system, compared with the extent of distribution and the degree of drug internalization.

The accurate delivery of the therapeutic drug to the appropriate tissue remains paramount to the efficacy of treatment and minimization of toxicity. In this instance, the blood-brain barrier may present a major physical obstacle for systemically administered agents [30]. However, preclinical models of $^{V}EDV_{Dox}$ using mouse xenograft models, and unpublished data on dog trials, have suggested good tumor penetration of $^{V}EDV_{Dox}$, evidenced from ^{123}I uptake. A substudy of $^{V}EDV_{Dox}$ bioavailability in this patient group would be beneficial.

5. Conclusion

In conclusion, this study demonstrated that $^{V}EDV_{Dox}$ can be administered safely to patients with recurrent GBM, with a maximum treatment dose of 5×10^9 $^{V}EDV_{Dox}$. Our results suggest that $^{V}EDV_{Dox}$ has minimal single agent activity. Nevertheless, this study is the first to examine this novel technology, and targeting EGFR remains a relevant strategy for future development. Further preclinical and biodistribution studies should be considered.

Conflicts of interest/disclosures

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