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Doxorubicin and irinotecan drug-eluting beads for treatment of glioma: a pilot study in a rat model

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Abstract Despite some progress in therapy, the prognosis of patients with malignant gliomas remains poor. Local delivery of cytostatics to the tumour has been proven to be an efficacious therapeutic approach but which nevertheless needs further improvements. Drug Eluting Beads (DEB), have been developed as drug delivery embolisation systems for use in trans-arterial chemoembolisation. We tested in a rat model of malignant glioma, whether DEB, loaded with doxorubicin or irinotecan, may be used for local treatment of brain tumours. Unloaded and drug loaded DEB were implanted into the brains of healthy and tumour bearing BD IX rats followed by histological investigations and survival assessment. Intracerebral implantation of unloaded DEB caused no significant local tissue damage, whilst both doxorubicin and irinotecan DEB improved survival time significantly. However, a significant local toxicity was found after the implantation of doxorubicin DEB but not with irinotecan DEB. We concluded that irinotecan appears to be superior in terms of the risk-benefit ratio and that DEB may be used for local treatment of brain tumours.

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1 Introduction

In view of an unchanged median survival time of 12–15 months after diagnosis, the prognosis of patients with malignant gliomas remains poor, despite improvements in microsurgery, volumetric imaging, radio- and chemotherapy. Therefore, the search for innovative therapy strategies including potent anti-tumour agents remains a major focus of brain tumour research. Despite an enormous research effort, intravenous administration of chemotherapeutics remains restricted by the presence of the blood–brain barrier and mechanisms of drug resistance and is accompanied by many side effects. To date, the efficacy of systemic chemotherapy has been proven only for temozolomide [1, 2].

Local delivery of cytostatics to the tumour circumvents the blood–brain barrier and may result in high drug concentrations at the tumour site [3]. A sustained delivery of an anti-tumour drug not only proved to be superior to single applications in terms of efficacy as well as of local toxicity but, given the recurrent nature of gliomas, rather appears to be mandatory in a serious clinical therapeutic approach [4–7]. Carmustine, delivered from polymeric wafers implanted locally at the tumour site after its microsurgical resection, has been demonstrated to be efficacious in clinical studies [8–10]. Although the basic efficacy of this therapeutic approach has therefore been shown, there are no other drugs for clinical use available. Furthermore, a significant prolongation of the median survival time of less than 2.5 months in patients treated with carmustine wafers [10, 11], illustrates all too clearly the need for further improvements of the therapy of gliomas.

The clinical studies also revealed that the therapeutic benefit from wafers is hindered by relatively common complications, e.g. cerebral oedema, intracerebral hypertension, seizures and cerebral abscesses [12]. The clinical

testing of another promising product for local glioma therapy, using paclitaxel and carboplatin released from liquid crystalline cubic phases, also revealed the occurrence of moderate to severe brain oedema in the patients [13]. The search continues therefore, for other agents locally applied to brain tumours by release from polymers or other carriers. Amongst the array of available chemotherapeutic agents, two potential candidates with promise are doxorubicin and irinotecan. Clinical trials with systemic administration of these drugs have shown limited results [14–16] despite their potent anti-tumour efficacy in vitro [17, 18]. The potential of both drugs to be applied locally by release from polymeric wafers, and the subsequent efficacy of these treatments have already been demonstrated in rodent models of malignant glioma. In the case of both drugs however, cytopathological changes, e.g. haemorrhages and necrosis of non-tumourous brain tissue, were experienced [6, 19–21]. This approach therefore, needs further improvement if doxorubicin or irinotecan are to be applied locally to brain tumours in future clinical studies.

Recently, Drug Eluting Beads (DEB), have been developed as drug delivery embolisation systems for use in transarterial chemoembolisation. The DEB are loaded with a cytotoxic drug for the purpose of treating a variety of tumours by blocking their feeding arteries and delivering the drug locally [22]. The DEB are made from a biocompatible polyvinyl alcohol (PVA) hydrogel that has been modified with sulfonate groups that allow the controlled loading and delivery of chemotherapeutic drugs. DEB loaded with doxorubicin received European approval in 2003 and are most commonly used for the treatment of hepatocellular carcinoma, liver metastases, cholangiomas and neuroendocrine cancers. The DEB may also be loaded with irinotecan, which are currently under investigation in a number of studies in the treatment of colorectal metastases to the liver. The aim of this study is to provide first insights into whether DEBs may be used for the local treatment of brain tumours, with a view to possible discovery of new and helpful variations and improvements in drug choice, dosage and application technique of this therapeutic approach. We assessed safety and dosage aspects by histological investigation of the reaction of the brain tissue to the implantation of DEBs and evaluated the impact of DEB treatment on survival in a rat model of glioma.

2 Materials and methods

2.1 Drug eluting beads

Unloaded DEB were obtained from Biocompatibles UK Ltd (DC Beads^{TM}, termed DC from herein, Biocompatibles UK Ltd, Farnham, UK). Manufacturing including drug loading is described elsewhere [22]. Briefly, beads were prepared by a redox-initiated inverse suspension free-radical copolymerisation of a polyvinyl alcohol macromer (modified with *N*-acryloylamino- acetaldehyde dimethlyacetal) with 2-acrylamido-2-methylpropanesulfonate sodium salt. The resulting beads underwent a series of solvent extractions for purification purposes and were then tinted blue (for ease of handling) using Reactive Blue 4 dye. The hydrogel beads were then extracted under boiling conditions in a high ionic strength aqueous solution to remove further residuals, mechanically sieved into size fractions and steam sterilised. Beads in the size range 100–300 μm were used in this study. DEB were used as a saturated suspension in 0.9% normal saline (DC) or water for injection (doxorubicin, irinotecan), respectively, resulting in corresponding drug doses of 0.038 mg/μl (doxorubicin) and 0.14 mg/μl (irino), respectively. Unloaded beads (DC) were used for implanting control animals. All handling of the DEB was performed under sterile conditions.

2.2 In vitro drug elution from DEB

Drug elution from the DEB has been well documented in the literature for both doxorubicin [22–24] and irinotecan [25]. Elution was measured using a T-apparatus ($n = 3$ for each DEB), an in vitro elution method designed to emulate release by diffusion and convection mechanisms as expected in tissue. The elution medium was PBS at 37°C, circulated through the T-apparatus by a peristaltic pump at a rate of 50 ml/min. The drug released into the PBS was measured by use of a flow-through cell in a Perkin Elmer Lambda spectrophotometer ($\lambda = 483$ nm for Doxorubicin and 369 nm for Irinotecan). The total dose of drug administered into the T-apparatus was 37.5 mg of Dox and 100 mg of Irinotecan. The half-life of drug elution was estimated by power law fitting ($M_t/M_0 = kt^{1/2}$, where M_t is drug elution at time t, M_0 is total drug loading in beads). For doxorubicin, $k = 0.009$; for irinotecan, $k = 0.081$.

2.3 Animals and implantation procedures

A total of 93 male and female BD IX rats, aged 11–12 weeks, were used for all experiments. The animals were obtained from the central animal laboratory of the Medical School, Hannover, Germany, and were kept under controlled environmental conditions with a standard laboratory diet and water available ad libitum. All animal husbandry and handling were conducted according to A-T-001-03 in compliance with the German Animal Welfare Act and was approved by the responsible governmental agency in Hannover. During the experiments, anesthesia was induced by i.p. ketamine (75 mg/kg) and medetomidine

(0.2 mg/kg). These studies were approved by the local animal care committee (Landesamt für Verbraucherschutz und Lebensmittelsicherheit, Oldenburg, Germany).

In order to induce the experimental gliomas, animals were injected with 8000 BT4Ca rat glioma cells suspended in 3 µl phosphate buffered saline. The cells were obtained from the Institute for cellular biology, University of Essen, Germany. Cells of the same passage were thawed, passaged one time, and harvested at sub-confluency immediately prior to implantation. The cell suspension was stereotactically implanted using a 10 µl gastight syringe (Hamilton, Bonaduz, Switzerland) fitted with a 26 gauge cannula 1 mm posterior and 3.4 mm lateral to bregma, at a depth of 5 mm, slowly over 4 min. Stereotactic implantation of the DEB was performed either into non-tumour bearing rats or on day 7 after the implantation of the tumour randomly assigning the animals to groups. The posterior and lateral stereotactic coordinates were identical to the implantation of the tumour cells. The DEB depot was applied in three steps in depths of 8–5 mm from bregma in order to minimize the volume related impact to the brain. A 50 µl gastight syringe fitted with a 19 gauge cannula (Hamilton, Bonaduz, Switzerland) was used. After each implantation, the skull was closed with bone wax.

2.4 Histological techniques

Rats were anesthetized with a lethal dose of ketamine (100 mg/kg) and medetomidine (0.3 mg/kg), perfused via the heart with paraformaldehyde, and the brains were processed for histological investigation. Ten micrometres coronal cryostat sections (HM 560 Cryo-star, MICROM International GmbH, Walldorf, Germany) were mounted serially onto slides.

Histological investigations were performed using an Olympus BX51 microscope equipped with cell*F imaging software (Olympus, Hamburg, Germany). Routine haematoxylin and eosin (H&E) staining was applied.

2.5 Survival

Following the implantation of tumour cells and 1 µl of DEB suspension, the animals were monitored twice daily. We already know from other experiments addressing the characterisation of our tumour model, that the rats usually showed normal behaviour and no signs of illness for at least 2 weeks; until the tumour growth significantly affects vital and/or predominant parts of the brain and their general condition rapidly deteriorates thereafter within less than 12 h. These rats, showing markedly decreased activity and reflexes and moving only when touched, were euthanized by perfusion. The day of euthanasia post-tumour cell implantation was recorded. Monitoring was performed by investigators blinded to the experimental groups. Following H&E staining, histological investigation was performed in order to verify successful implantation of tumour and DEB and in order to demonstrate efficacy mechanisms and possible side effects of the eluted drugs.

2.6 Statistics

Kaplan Meyer survival statistics were calculated from the day of euthanasia and the curves were plotted and compared using GraphPad PRISM and the included log-rank test (v 4.03; GraphPad Software, San Diego, CA).

3 Results

3.1 In vitro drug elution from DEB

As previously demonstrated in the literature [22, 23], it can be seen that doxorubicin elution from the DEB using this in vitro elution method is very slow, with a half life of some 3000 h (Fig. 1). This is somewhat substantiated by recent studies on explanted porcine liver samples that had been embolised with doxorubicin DEB for approximately 90 days [26]. In an analysis of the tissue using microspectrofluorimetry, it has been demonstrated that drug is still eluting into the tissue, and significant amounts still remaining within the beads, at the 90 day implantation time point [27]. Irinotecan elution from DEB is faster than for doxorubicin [25], with an estimated half-life of around 38 h (Fig. 1). This is due to a very much weaker interaction between the irinotecan molecules themselves once loaded into the DEB, compared to the drug–drug interaction that occurs within the doxorubicin DEB [23].

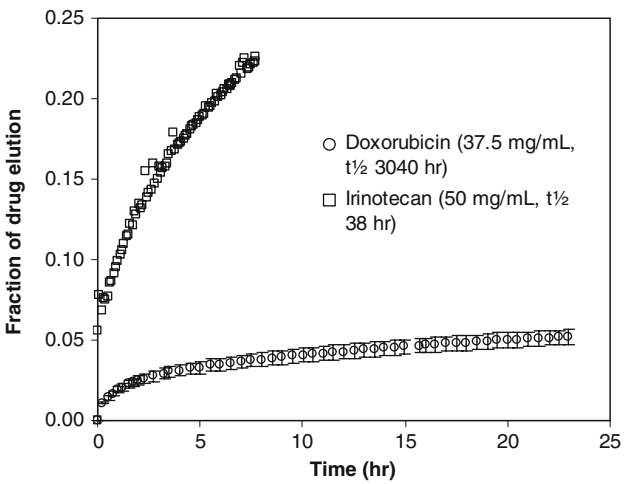

Fig. 1 In vitro release of doxorubicin (37.5 mg/ml) and irinotecan (50 mg/ml) DEB in PBS using a T-apparatus ($n = 3$)

3.2 Biocompatibility—implantation of unloaded DEB into healthy brain

Histological investigation of different volumes of unloaded DEBs implanted for different time periods up to 60 days indicated no significant brain tissue damage. An overview of the implantation site ($n = 3$) 14 days after the implantation of 1 µl unloaded DEBs is shown in Fig. 2a. A detailed magnification of the same slide (Fig. 2b) revealed only a minor cellular reaction, most probably consisting of gliotic tissue, macrophages, some necrotic tissue, and few haemosiderin deposits in between the DEBs, as far as HE staining allows cell classification. Considering this restriction, only very few cells resembling granulocytes and lymphocytes were detected, indicating no inflammation or rejection. Although not investigated quantitatively, it appears that after 60 days (Fig. 2c, $n = 3$) the cellular reaction is markedly less than after 14 days. Necrotic tissue (pale pink areas without cells or with highly disintegrated cells) was almost completely replaced by gliosis (cellular structures).

3.3 Local toxicity—implantation of drug loaded DEB into healthy brain

Healthy rats ($n = 12$) were implanted with 1, 2, and 3 µl doxorubicin or irinotecan DEB suspension, respectively. Half of the animals was perfused immediately after the implantation and the other half was perfused 14 days later. Figure 3 shows the brain tissue reaction to the implantations. Although implantation of volumes of 3 µl or more were technically feasible in this experimental setup, histological investigation revealed significant increasing brain tissue damage with increasing drug dose. Large areas of cerebral haemorraghes and necrotic brain tissue were found especially in the animals implanted with 3 µl of doxorubicin DEB. Including the massive cellular infiltration, almost the entire hemisphere was affected by the implantation of 3 µl doxorubicin DEB. However, these animals showed no signs of impairment of their general condition over the experimental period of 14 days. In another experiment, addressed to possible general side effects of cerebral implantation of doxorubicin DEB, 12 healthy rats were implanted with 5 µl of doxorubicin DEB. Nine of these animals had to be euthanised from day 6 onwards due to severe neurological symptoms or significant impairment of their general condition. Three animals survived the observation period of 60 days. The calculated median survival time in this experiment was 26.5 days. The histological investigation in this experiment revealed mostly the same findings as described above, but to a higher degree than in the animals implanted with 3 µl.

Figure 3 also demonstrates that the implantation of smaller volumes of irinotecan DEB caused markedly less damage to the brain tissue. Only minor accumulations of erythrocytes, mostly within the DEB depot, therefore probably resulting from the implantation procedure itself, were found 14 days after implantation of irinotecan DEB. Cellular infiltration was confined directly to the margin of the implantation site. No necrosis of brain tissue distant from the irinotecan DEB was detected.

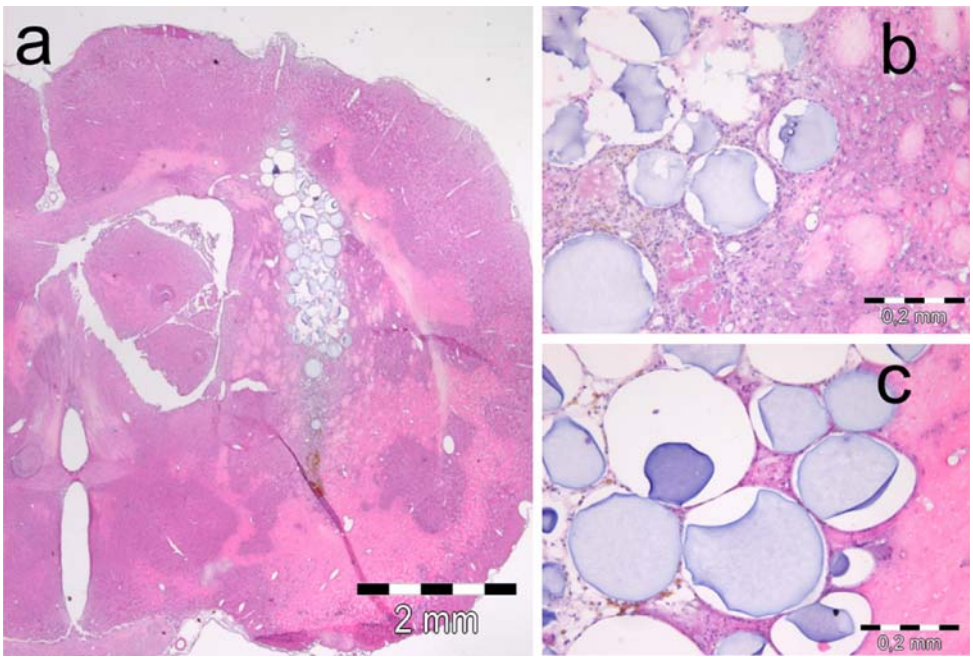

Fig. 2 **a** Shows a cross section (HE staining) through the brain hemisphere 14 days after implantation of unloaded DEB (DC). The microspheres are distributed along the injection canal lateral to the cerebral ventricle. HE staining revealed no significant inflammation, oedema or hemorrhage, the ventricle is not compressed, there is no midline shift. At higher magnification, no significant cellular reactions except a mild gliosis is evident around the DEBs neither after 14 days (**b**) nor after 60 days (**c**)

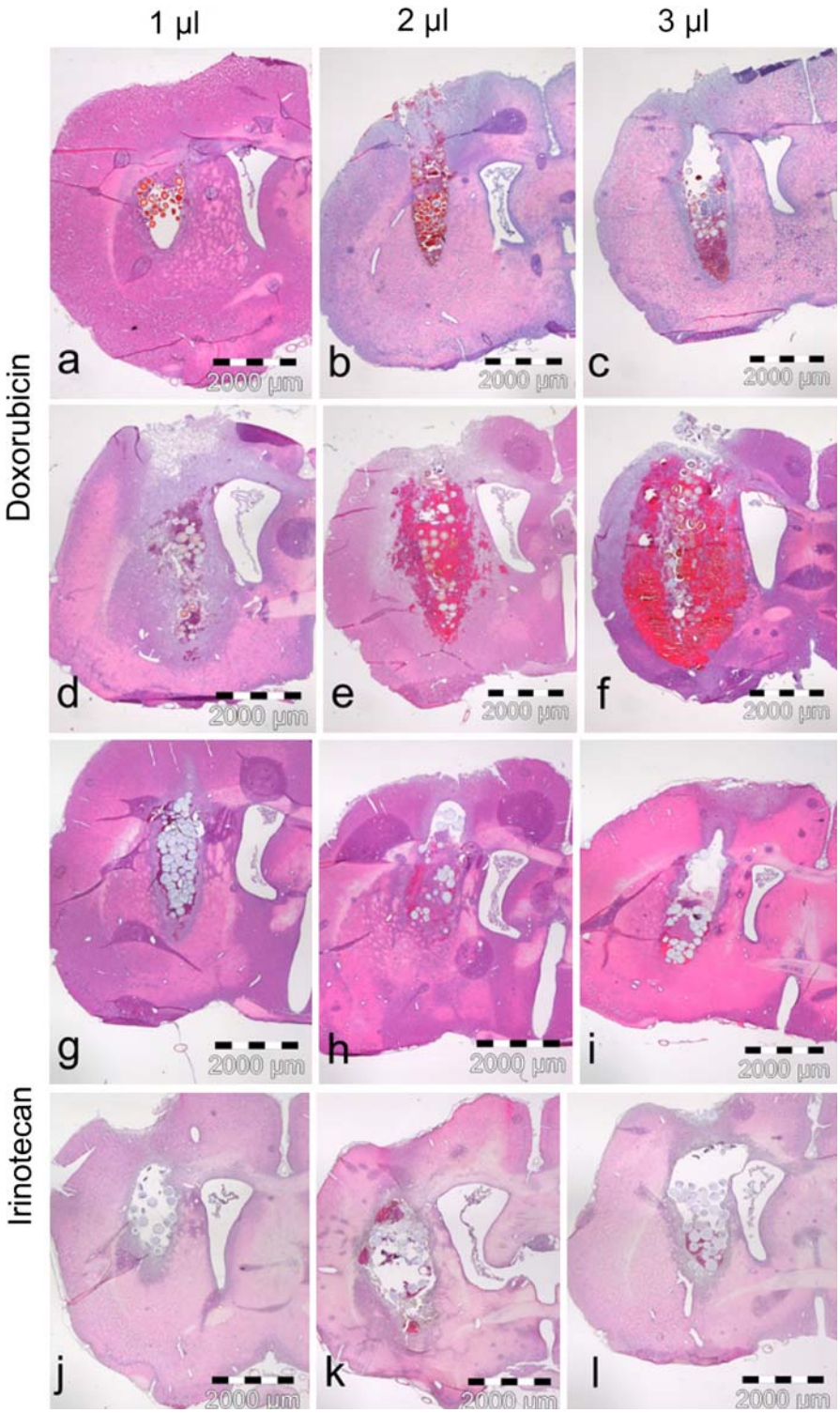

Fig. 3 Cross sections (HE staining) after the stereotactic implantation of different volumes of DEB into the rat brain. **a**, **b**, **c** and **g**, **h**, **i** show the tissue reaction immediately after implantation of doxorubin and irinotecan beads, respectively. A local tissue disruption resulting from the stereotactic implantation procedure but no significant hemorrhages can be seen. **d**, **e**, **f** and **j**, **k**, **l** show the corresponding tissue reaction after a 14-day implantation period. After implantation of doxorubicin DEB (**d–f**), haemorrhages at the implantation site can be observed, which are moderate after implantation of 1 µl and most expressed following implantation of 3 µl. A total of 14 days after the implantation of irinotecan DEB (**j–l**), only minor hemorrhagic areas were observed. Empty areas within the implantation site result from DEB lost during the histological preparation. Representative microphotographs, $n = 12$

3.4 Efficacy—survival

Applying the criteria for euthanasia, animals ($n = 60$) were euthanised as follows: Tumour only: day 14–17; DC implanted animals: day 14–22; irinotecan: day 14–26; doxorubicin: day 14–38. The survival curves are presented in Fig. 4. The calculated median survival times are: Tumour only: 16 days, DC: 17 days, irinotecan: 21 days, doxorubicin: 21 days. All curves of the beads-treated animals are significantly different from the untreated tumour group. The curves of the DEB treated animals are significantly different from the DC beads treated group (*P* values

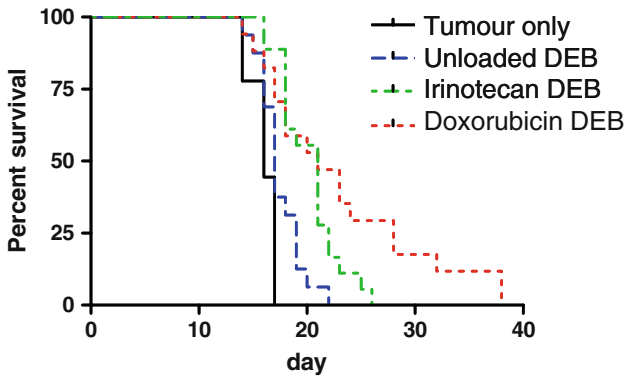

Fig. 4 Survival curves of treated and untreated glioma rats. Tumour only: $n = 9$; unloaded DEB (DC), $n = 16$; irinotecan DEB, $n = 18$; doxorubicin DEB, $n = 17$

DC vs. doxorubicin: 0.0028; DC vs. irinotecan: 0.0018) but the curves of doxorubicin and irinotecan are not significantly different from each other. All animals included in the survival calculations were histologically verified for successful implantation of tumour and beads.

3.5 Efficacy—histology

The photomicrograph of Fig. 5a shows the typical histomorphological structure of the untreated malignant glioma in the rat model used in this study. It revealed high cellularity, polymorphic glial tumour cells with polygonal nuclear shape and both a variable and irregular nuclear-cytoplasmatic ratio as well as numerous mitotic figures. The tumour exhibited areas of oedema, pycnotic cells, and total necrosis of variable extent, which were in places surrounded by structured extended glioma cells or, more often, were infiltrated with cells resembling leucocytes. Parenchymal structures were displaced and the ventricles were compressed by the tumour mass. The tumours showed a high vascularity with larger vessels predominantly proliferating in the ventral regions. Vessel lumen were often irregularly expanded or damaged, causing small haemorrhages.

Further animals ($n = 3$) were processed for histological assessment of the tumour morphology at day 7 after inoculation of the cell suspension. Figure 5e shows a corresponding photomicrograph, where the distribution of the growing tumour tissue along the implantation path could be observed.

In Fig. 5b–d, the photomicrographs of representative animals of every DEB treated group are presented. The DEB could basically be observed throughout the entire tumour tissue but not evenly distributed. 1 µl of suspension contains approximately 25–35 DEB. The majority of DEB was found in the ventral, striatal regions at the site of implantation. Single beads were located as well as deposits of several beads. With respect to the tumours' longitudinal dimension of approximate 5–14 mm, one slice (thickness 10 µm) as depicted here, does not reflect the actual number of implanted beads.

Microscopical investigation of HE stained slices was also performed in order to histologically demonstrate efficacy mechanisms of the eluted drugs within the tumour tissue. In Fig. 5f, unloaded DEB (DC), implanted in tumour tissue (dark blue tissue with visible cell structures) are shown. No cellular reaction except for a minor circular formation of the tumour cells around the beads could be observed either in the tumour nor in the adjacent non-tumourous brain tissue (fibrous, pale blue tissue). However, in the doxorubicin and irinotecan DEB treated animals, several alterations of tumour and brain tissue could be observed. Regarding the cellular mechanism, most of these findings described below were basically similar to untreated tumours, but in the tumours of treated animals these alterations could be observed to a much greater extent. Furthermore, these alterations were found much more pronounced in the vicinity of the DEB.

Most frequently, in both drug treated groups large areas of tumour tissue disintegration were observed. Disintegration was characterized by loosened cell contacts, rounded cell shapes, markedly reduced cell density, and the onset of nuclei disintegration (Fig. 5g).

The most outstanding histological findings in the drug treated animals were areas of haemorrhages, indicated by erythrocytes and disrupted tumour blood vessels (Fig. 5h). In the doxorubicin treated animals, these areas were markedly more pronounced than in the irinotecan treated animals and the extent of the haemorrhages was most exceedingly pronounced in the vicinity of DEB deposits. As described above, the majority of DEB were found in the ventral, striatal regions at the site of implantation. In the doxorubicin DEB treated animals, severe haemorrhages could be also observed in adjacent non-tumourous brain tissue (Fig. 5d), which was not observed in irinotecan DEB treated animals.

4 Discussion

Biocompatible sulfonate-modified polyvinyl alcohol (PVA) hydrogel-based DEB loaded with doxorubicin are in clinical use for transarterial chemoembolisation of malignant hypervascularised tumours. This and previous studies have shown that both drugs can be eluted from beads in vitro in a sustained fashion over days to weeks, although doxorubicin release is much slower than irinotecan. The present study examined whether such DEB loaded with doxorubicin or irinotecan may also be used for local treatment of brain tumours.

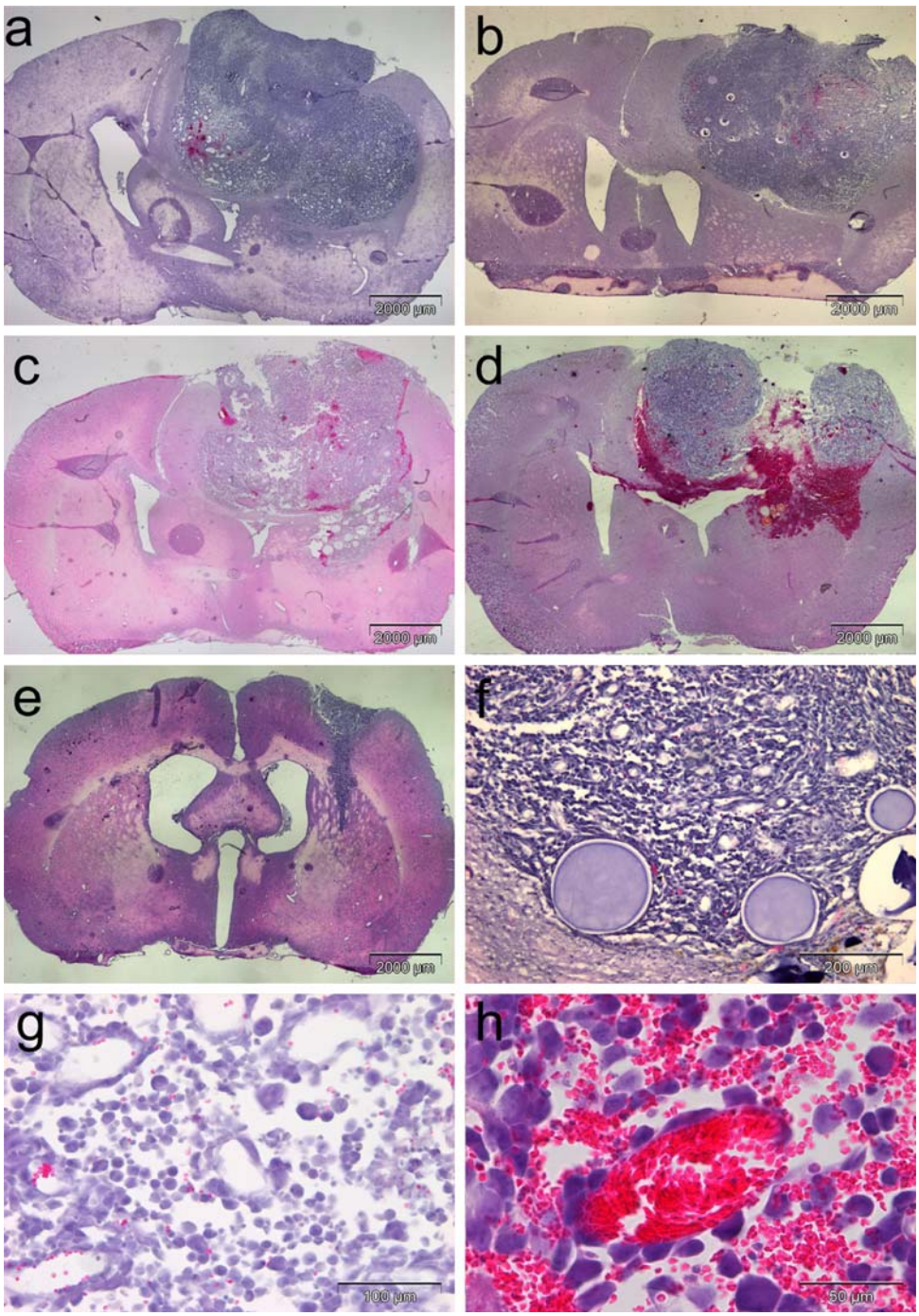

Fig. 5 Cross sections of the brains of treated and untreated glioma animals, HE staining. **a** Untreated glioma; **b** animal implanted with unloaded DEB; **c** tumour treated with irinotecan DEB; **d** tumour treated with doxorubicin DEB; **e** shows the tumour size at the time point of implantation with DEB; **f** empty unloaded DEB 14 days after implantation into the tumour showing no cellular reactions at the implantation site; **g** disintegration of tumour tissue in drug treated animals. 20× objective; **h** intratumoural haemorrhage in doxorubicin DEB treated animal. Erythrocytes and disrupted capillary. 40× objective

In a rat model of malignant glioma, we showed that the intracerebral implantation of unloaded DEB caused no significant local tissue damage and that doxorubicin or irinotecan DEB improved survival time significantly. However, a significant local toxicity was found after the intracerebral implantation of doxorubicin DEB but not with irinotecan DEB at the concentrations under investigation.

In our studies, we used a syngeneic model of malignant glioma [28, 29]. The syngeneity may be of some advantage in comparison to non-syngeneic animal tumour models, in which human glioblastoma or mouse gliosarcoma lines are implanted into rats, because the host versus graft immune reaction might interfere with tumour growth and could add a confounding factor to the assessment of any therapeutic approach [30, 31]. Accordingly, in a similar study

addressed to the local application of anti-tumour agents in the C6 model, alloimmune rejection of the tumour was observed, showing the limitations of a non-syngeneic glioma model [32].

The biocompatibility of the doxorubicin or irinotecan DEB has already been demonstrated in vitro and in vivo studies, e.g. after injection into the liver [25, 26]. Furthermore, clinical studies revealed no significant side effects following the intravascular injection of the DEB into liver tumours [33, 34]. Supporting these results, our experiments revealed only a minor cellular reaction following intracerebral implantation of unloaded DEB into normal brain tissue. Similar reactions were found in other studies testing the biocompatibility of polymeric wafers or microspheres in the brain [35, 36].

Comparing our findings in the animals implanted with unloaded DEBs (Fig. 2) and those in animals implanted with drug loaded DEBs (Fig. 3), it is very obvious that the reaction of the brain tissue is exerted by the drug and not by the carrier. Doxorubicin DEB caused a significant tissue reaction, i.e. necrosis and haemorrhages resulting from damage of the capillary endothelia. Comparing the extent of the haemorrhage at different implantation volumes, these side effects of doxorubicin appear to be dose-dependent. These findings are in agreement with previous reports studying the histological reaction of brain tissue to doxorubicin released from polymeric wafers [6]. Animals implanted with irinotecan did not show such side effects in our investigations. In contrast, Storm et al. found cytopathological changes following the intracerebral release of camptothecin (irinotecan is a water-soluble analogue of this drug) at distances up to 3 mm from the implantation site, but they were not able to distinguish between toxicity caused by polymers loaded with 20% or with 50% of the drug, respectively [19]. Another study demonstrated severe CNS toxicity following the application of free irinotecan, whereas prolonged exposure to nanoliposomal irinotecan, even at higher dosages, resulted in no measurable CNS toxicity [7]. These apparently different results from our and other similar studies are not contradictory. They rather point out the impact of not only the drug dose but also of different carriers. This issue needs further pharmacokinetic or toxicologic investigations for clarification. Considering possible side-effects to be related to pharmacokinetic parameters, such investigations should reflect the situation in patients much more closely than in rat models as previously claimed in a similar fashion [6].

The survival statistics indicated a significant effect of both drugs at the investigated concentrations. These results are in agreement with previous studies, demonstrating either the in vitro efficacy of the drugs on BT4C cells or other in vitro glioma models [17, 37] and the anti-tumour effects of the drugs or analogues after local delivery to the brain either from implanted polymeric wafer or by direct intracerebral infusion [6, 19–21, 37]. Although we found the longest survival time in animals treated with doxorubicin, the effect of both drugs on survival differed not statistically from each other. It may be that given the more rapid release of irinotecan from the DEB compared to doxorubicin, the sustained period of local delivery in vivo is somewhat shorter which may impact on the overall survival time of the rats in the irinotecan DEB group. Future studies should investigate combination of both drugs which has been shown to have synergistic efficacy [38, 39]. Given an efficacious release of both drugs but considering significant local side effects which were only seen after application of doxorubicin, irinotecan appears to be superior in terms of the risk-benefit ratio. Although this has been concluded before in other investigations evaluating the application of DEB chemoembolisation [40], the occurrence of the cytotoxic local side effects in this study appear to be related to the pharmacokinetic aspects of the drug-device combination. The small and varying size of DEBs allows specific variations of dose adjustment or post surgical placement, or mixing with further carrier substances. Therefore, the drawbacks experienced in this work with doxorubicin, i.e. local toxicity, could be potentially overcome compared to larger sized products, by formulation to alter the local pharmacokinetics.

The DEB under study are injectable because of the small particle size (in the range 100–300 μm in diameter, albeit still an order of magnitude larger than drug delivery nanoparticulate systems which are designed for delivery via the systemic circulation [41]). With regard to a possible clinical application, we consider this ability to be injected directly into the tissue an advantage in comparison to polymeric wafers, which can only be loosely placed into the cavity after tumour resection. Injection allows a more targeted application and should increase the local drug concentration because of the direct contact between tumour tissue and polymeric carrier. Furthermore, surgically non-accessible tumour regions may therefore be treated. Moreover, injectable, small sized, drug-eluting polymers have already been investigated. In a series of pre-clinical studies, the efficacy of 5-fluouracil releasing microspheres has been demonstrated in rat models of malignant glioma [42–44]. However, in clinical trials, the application safety of the 5-fluouracil releasing microspheres was demonstrated but they failed to show efficacy in terms of survival time [45, 46]. According to our experimental results we suggest that the use of DEB loaded with either irinotecan or doxorubicin might be more effective in a clinical setting.

5 Conclusion

In this pilot study, we confirmed the known advantages of a local, sustained chemotherapy for DEBs in a rat model of glioma. We experienced drawbacks using doxorubicin DEBs but we also obtained clear indications of advantages using irinotecan DEBs compared to previous studies using other products. With the versatile formulation capabilities of the DEBs, we continue our research, in particular on application safety and dosage variation, because we believe that DEBs releasing doxorubicin or irinotecan have the potential to be part of a highly efficacious combined surgical and local chemotherapeutic treatment of malignant gliomas.

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