Compatibility of irinotecan-loaded DC Bead with different volumes and types of non-ionic contrast media

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ABSTRACT

Objectives Irinotecan-loaded microspheres are used for simultaneous embolisation and chemotherapy of liver metastases of colorectal carcinoma. The aim of the study was to evaluate the compatibility of recently introduced DC BeadM1 (bead size 70–150 µm) loaded with irinotecan after admixture with different types and volumes of non-ionic contrast media over a maximum period of 24 h and storage at room temperature.

Methods Test suspensions were prepared by loading 2 mL DC BeadM1 with 100 mg irinotecan within 2 h. The loading efficiency was determined by measuring the concentrations of irinotecan in the excess solutions via a reversed phase high pressure liquid chromatography (RP-HPLC) assay with ultraviolet detection. The compatibility of irinotecan-loaded DC BeadM1 with different types and volumes of contrast media was studied by mixing 2 mL loaded bead slurry each with up to four different volumes (5, 10, 20, 30 mL) of seven different contrast media. Samples were withdrawn after 30 min, 1, 2, 4, 8 and 24 h. Admixtures were stored light protected at room temperature over the observation period. The concentrations of eluted irinotecan were measured in triplicate samples using the RP-HPLC assay.

Results Mixing of irinotecan loaded beads with non-ionic contrast media decreased the irinotecan loading efficiency between minimum 2.5% and maximum 17% over the observation period of 24 h. The rate and amount of irinotecan eluted from the beads varied relying on the type and volume of contrast medium admixed. However, no further elution or degradation was observed after the rapid release during the first 8 h.

Conclusions Because of the rapid and extensive release of irinotecan, it is not recommendable to prepare admixtures of irinotecan-loaded DC BeadM1 with contrast media in centralised cytotoxic preparation units in advance. Admixture should be performed with the smallest possible amount by the radiologists immediately prior to the delivery procedure.

INTRODUCTION

Colorectal carcinoma (CRC) is a widespread type of cancer, reported to be the second and third most often diagnosed cancer in female and male patients, respectively.¹ Although treatment options improved during the past years in the developed countries, mortality is still high.² Besides surgery of the localised carcinoma, multimodality therapy comprising chemotherapy regimens, radiation and palliative care are used to treat advanced CRC.³

Transarterial chemoembolisation (TACE) is an outstanding technique used to treat liver cancer and also liver metastases of CRC and other tumours. By

local administration of drug-eluting microspheres, high concentrations of antineoplastic drugs and embolisation of the arteria supplying the tumour are accomplished. Simultaneous administration of the embolising and pharmacological principles in the form of a drug device combination, like DC Bead, represents the most advanced type of TACE.⁴ DC Bead allows the load of cationic drugs and the controlled release of the cytotoxic agent within the tumour bed. The DC Bead microspheres consists of a polyvinyl alcohol backbone cross linked with unsaturated 2-acrylamido-2-methylpropane sulfonate sodium salt to obtain negatively charged sulfonate moieties, which allow the loading of cationic drugs. Among the typically loaded antitumour drugs are doxorubicin, epirubicin, topotecan and irinotecan, each in the hydrochloride salt form. The positively charged drugs are loaded and released in a controlled manner through an ionic charge-charge interaction. The drug-loaded beads are administered via a microcatheter after mixing with non-ionic contrast media (CM) to guide the injection and to facilitate the selective delivery of the drug eluting beads (DEB) to the targeted tumour.

Irinotecan is a semisynthetic analogue of camptothecin acting as topoisomerase-1-inhibitor after systemic and locoregional administration.^{5, 6} It is used in combination with fluorouracil and monoclonal antiepidermal growth factor receptor or anti-vascular endothelial growth factor antibodies in patients suffering from metastatic or unresectable CRC.⁵ Irinotecan (CPT-11) is rapidly metabolised by hydrolysis of the carbamate ester moiety by liver carboxylesterase to SN-38. Irinotecan and its active metabolite SN-38 bind to the topoisomerase 1–DNA complex (specifically in the S-phase of the cell cycle) forming a triple complex, which prevents religation of DNA strands, and overlaps with the replication fork. Thereby, DNA replication is stopped, and the irreversible damage results in cell death.⁷ The intact lactone ring of irinotecan and its derivatives is a prerequisite for cytotoxic activity. However, the lactone structure is sensitive to pH changes, and undergoes reversible hydrolysis. Acidic pH values (pH<3.5) favour the lactone ring form while alkaline conditions induce ring opening and lack of cytotoxic activity.^{7–9} High loading efficiency and adequate stability of intact irinotecan to the DC Bead microspheres (bead size 100–300 µm) has been proven by in vitro studies some years ago.^{8, 10} The beads retain the lactone stability and prolong the half-life of the lactone form, which can provide an improved anticancer effect.⁸ Mixing of 2 mL irinotecan-loaded beads (DEBIRI) (bead size

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100–300 μm , 300–500 μm) with 6.5 mL non-ionic contrast media rapidly decreased the loading efficiency of irinotecan by 5%–10%.⁹ More recently, DC BeadM1 (bead size 70–150 μm) was introduced in the market. The aim of these experiments was to evaluate the compatibility of the novel bead size 70–150 μm loaded with irinotecan (100 mg/2 mL) and mixed with seven different non-ionic contrast media, which are commonly used by radiologists to guide the administration of DEBIRI to the targeted tumour site. Compatibility was planned to be studied with up to four different volumes (5, 10, 20, 30 mL) of non-ionic contrast media over a maximum period of 24 h while stored at room temperature.

MATERIAL AND METHODS

DC BeadM1 (bead size 70–150 μm , lot: V10647-DEV-(02/2017) was received from Biocompatibles, BTG, Camberley, UK, as a grant. The DC Bead vials were labelled as R&D only, Not for Human Use. Each 10 mL DC Bead vial contains 2 mL beads and 6 mL physiological buffered saline.

Commercially available Irinotecan Accord 20 mg/mL, 25 mL, Accord Healthcare, Sage House, 319 Pinner Road, North Harrow, Middlesex, UK, (lot: P11760-(09/2015) contains nominally 500 mg irinotecan HCl 3 H₂O.

The samples were prepared in Omnifix polypropylene (PP) syringes Luer Lock Solo 20 mL (lot: 2B24048-(02/2019), B Braun Melsungen AG, Melsungen, Germany) or Original Perfusor syringes 50 mL (lot: 13L1982027, B Braun Melsungen AG, Melsungen, Germany). The syringes were used as primary packaging material.

The non-ionic contrast media used in this study were Accupaque 350 (100 mL, CH-B: 12322355-(12/2016), GE Healthcare Buchler, Braunschweig, Germany; iohexol-containing Accupaque is also marketed under the trade name Omnipaque), Imeron 400 MCT (200 mL, CH-B: 3110592-(09/2018), Bracco Imaging Deutschland, Konstanz, Germany), Optiray 300 (50 mL, CH-B: 13J2685-(09/2016), Mallinckrodt Deutschland, Hennef, Germany), Optiray 350 (50 mL, CH-B: 13G09214-(06/2016)), Solustrast 350 (50 mL, CH-B: 3G09214-(07/2018), Bracco Imaging Deutschland, Konstanz, Germany), Ultravist 370 (50 mL, CH-B: 41872C-(02/2017), Bayer Vital, Leverkusen, Germany) and Xenetix 350 (50 mL, CH-B: 13WF048F-(10/2016), Guerbet, Sulzbach, Germany).

HPLC assay

The irinotecan concentrations were determined by using a previously published, validated reversed-phase HPLC method.⁶ The HPLC system consisted of a Waters 510 HPLC pump, a Waters PDA-Detector 996 and a Waters Autosampler 717plus. Waters Empower pro, Empower² software, V6.10.01.00 was used to acquire and integrate the data. The separation was performed with the PerfectChrom 100CN column, particle size 5 μm , 250 mm $\times$ 4.6 mm (MZ-Analysentechnik, Mainz, Germany).

The mobile phase used consisted of 75% 0.02 M potassium dihydrogen phosphate solution (2.72 g KH₂PO₄ (lot: AM0444477 402, Merck, Darmstadt, Germany) dissolved in 1 L water HPLC Gradient Grade (lot: 4Q009403, 2.5 L, AppliChem, Darmstadt, Germany)) plus 25% of acetonitrile HPLC Gradient Grade (lot: 134622, 2.5 L, Promochem, Wesel, Germany). The injection volume was 20 μL and the flow rate 1.0 mL/min. The detector wavelength was set at 225 nm and the run time at 15 min. Under these conditions, the retention time of lactone-ring-closed irinotecan amounted to about 9 min.

Calibration was performed with eight concentrations of irinotecan solutions ranging from 15 to 200 $\mu\text{g/mL}$ and threefold

injection. The resulting calibration curve constructed from plots of peak area versus concentration showed linearity with a correlation coefficient of 0.9982.

Intraday precision of the HPLC assay was determined by five-fold injection of three standard concentrations of irinotecan solutions 50, 110 and 175 $\mu\text{g/mL}$ on the same day. The relative SDs amounted to 0.63% for 50 $\mu\text{g/mL}$, 0.66% for 110 $\mu\text{g/mL}$ and 2.7% for 175 $\mu\text{g/mL}$.

In order to determine interday precision, freshly prepared irinotecan solutions of the concentrations 30, 50, 100 and 150 $\mu\text{g/mL}$ were injected four times on five different days. The interday precision given as relative SD (%) amounted to 1.6% for 30 $\mu\text{g/mL}$, 2.5% for 50 $\mu\text{g/mL}$, 2.4% for 100 $\mu\text{g/mL}$ and 0.2% for 150 $\mu\text{g/mL}$.

Loading of DC BeadM1 with 20 mg/mL irinotecan hydrochloride solution (100 mg nominal dose)

The content of a DC BeadM1 vial was transferred to a 20 mL PP syringe (when 5 or 10 mL contrast media were added) or to a 50 mL syringe (when 20 or 30 mL of contrast media were added) via an 18-gauge needle. The packing solution was removed via a 5 μm filter needle until receiving a visually dry bead slurry mixture. Five millilitres of irinotecan infusion concentrate (ie, nominal dose 100 mg) were added to the DC Bead slurry in the PP syringe, and the admixture was agitated in a controlled manner (inverting the syringe 10 times). During the following loading process, admixtures were not agitated. Each test suspension was prepared in triplicate. In total, 51 DC BeadM1 vials were loaded with irinotecan hydrochloride (50 mg/1 mL beads). According to the calculated value and experimental results, the sulfonate sites in 1 mL beads are saturated with 50 mg irinotecan through charge-charge interaction, and further addition does not increase the loading efficiency.¹⁰

After 2 h of loading, the beads had settled down in the syringes, and the excess solution was removed through a 5 μm filter needle. In order to maintain the hydration of the loaded DC Bead, 2 mL of water for injection (WFI) (Aqua ad iniectionem, 50 mL, lot: S1311199 (31/08/2017), Department of Pharmacy, University Medical Center, Mainz, Germany) were added to each syringe, the syringe closed by a combi stopper and again inverted 10 times. DEBIRI were stored at room temperature under light protection (covered with aluminium foil) over a period of 24 h.

From the excess solutions removed after the loading procedure, 0.5 mL samples were withdrawn via a 5 μm filter needle into 1 mL BD Luer-Lok tip, and the concentration of irinotecan was measured by HPLC. Prior to the HPLC assay, samples were diluted 1:4 with 0.9% NaCl solution (Infusion Solution, 100 mL, freeflex infusion bag, lot: 13HBS051 (01/2016), Fresenius Kabi, Bad Homburg, Germany) in order to fit the calibration curve. Samples were acidified with 10 μL 1% H₃PO₄ (85% orthophosphoric acid, lot: 3R004802, AppliChem, Darmstadt, Germany, diluted to 1% phosphoric acid with water HPLC Gradient Grade) to pH 3.5, thereby favouring the lactone form of irinotecan. Samples were assayed in triplicate, and the percentage rate of irinotecan loaded calculated:

Loading rate (%)

$$= \frac{\text{initial drug concentration in solution} - \text{residual drug concentration in solution}}{\text{initial drug concentration in solution}} \times 100 \quad (1)$$

Compatibility of irinotecan-loaded DC BeadM1 with different non-ionic contrast media

To each syringe containing a suspension of DC BeadM1 in 2 mL WFI, the predetermined volumes of the seven different contrast media were added, and the admixtures were agitated in a controlled manner by inverting the syringe 10 times at each predetermined interval in order to measure the amount of irinotecan eluted into the injection admixture (WFI and non-ionic CM). During the observation period, the test suspensions were stored light protected at room temperature. 0.5 mL aliquots of the supernatant solution were withdrawn via a 5 µm filter needle after 30 min, 1, 2, 4, 8 and 24 h of storage. Aliquots were diluted 1:25 with 0.9% NaCl solution, acidified with 10 µL 1% H₃PO₄, and assayed in triplicate by HPLC. The percentage rate of irinotecan remaining loaded in the beads was calculated by the equation:

$$\text{Percentage rate of irinotecan remaining loaded after admixture with CM (\%)} = \frac{\text{drug concentration in solution before admixture} - \text{drug concentration in solution after admixture}}{\text{drug in solution before admixture}} \times 100 \quad (2)$$

RESULTS

The average loading level of irinotecan measured was 99.58% per 2 mL DC BeadM1, varying from 99.47% to 99.73%. The loss of individual beads during the loading procedure was minimal, and only minimal differences were observed between the measured concentrations and the nominal concentration of 100 mg irinotecan per 2 mL DC BeadM1 loaded.

When up to four different volumes of seven different contrast media were admixed to the irinotecan-loaded DC BeadM1 suspensions, significant amounts of irinotecan were eluted depending on the type and volume of contrast medium added. In addition, the type and volume of contrast medium added, determined the elution rate. When 5, 10, 20 and 30 mL of Optiray 300 or Optiray 350 were admixed to irinotecan-loaded DC BeadM1, after a period of 30 min, about 1%–2%, 3%, 4%, and 8%–9% of the irinotecan was eluted (see figures 1 and 2). The higher the volume of Optiray 300 or Optiray 350 admixed was, the more rapid irinotecan was eluted from the beads. Over the next 8 h, the percentage rate of irinotecan released went up to

2%, 5%, 7%–9% and 12%–16%. After 8 h, the equilibrium of the exchange was almost achieved. During the following 16 h, only small additional amounts of irinotecan were eluted.

When 20 or 30 mL of Imeron 400 MCT, Ultravist 370, Solutrast 370 and Xenetix 350 were admixed to irinotecan-loaded DC BeadM1, the eluted amount of irinotecan increased in each case when the bigger volumes of contrast media were used (compare figures 3 and 4). Irinotecan was released in large part after 8 h, and only small additional amounts were released until to the end of the observation period of 24 h.

For Accupaque 350, only one scenario was tested. Admixing 30 mL of Accupaque 350 to irinotecan-loaded DC BeadM1 caused the release of 4% irinotecan after 30 min and 7% after 8 and 24 h.

In figure 4, the amounts of irinotecan eluted after admixing the same volume, that is, 30 mL, of each contrast medium to the loaded beads are given in order to illustrate the influence of the type of contrast media admixed. About 3%–5% of irinotecan were released after 30 min and 5%–7% after 24 h when Imeron 400 MCT, Accupaque 350 and Solutrast 370 were added. However, in the case of Xenetix 350, the amount of irinotecan released increased from 5% after 30 min to 12% after 24 h of admixture. When Optiray 350, Ultravist 370 and Optiray 300 were admixed, the initial release amounted to 7%–8%, and increased to 14%–17% after 24 h. The differences in rate and amount of irinotecan released are to be explained by different osmolalities and viscosities of the contrast media products (compare table 1). No degradation products of irinotecan were detected in HPLC chromatograms of the admixtures. However, because of the rapid release of irinotecan, compatibility of the admixtures of DEBIRI with contrast media is not given.

DISCUSSION

Prior to the delivery via a microcatheter, drug-loaded microspheres have to be admixed with contrast media in order to guide the administration. There are different factors known to influence the compatibility of drug-loaded beads with contrast media. During the compatibility studies, the bead size (70–150 µm) and the type and amount of drug-loaded (irinotecan, 100 mg/2 mL beads) remained unchanged whereas the type and volume of contrast media varied. These parameters were chosen because small bead sizes are preferably used nowadays, and irinotecan is known to be more rapidly eluted after

Figure 1 Percentage rate (%) of irinotecan eluted from DEBIRI after mixing with different volumes of Optiray 300. Error bars indicate the relative SD.

Figure 2 Percentage rate (%) of irinotecan eluted from DEBIRI after mixing with different volumes of Optiray 350. Error bars indicate the relative SD.

admixture with contrast media than doxorubicin.^{9–11} Various types and volumes of contrast media were tested with regard to clinical practice. The volume of contrast media used to administer 2 mL of beads depends on the clinical situation. With an eye to clinical practice, 5–30 mL of contrast media was chosen to be tested. Blank or reference solutions were not tested because it is well known that irinotecan is not released when the loaded irinotecan beads are placed in deionised water.^{8–10} In order to determine the elution rate of irinotecan in the admixtures, samples were withdrawn at different predetermined time intervals up to a period of 24 h. Thereby, the influence of the type and volume of contrast media on the elution rate got obvious.

There are no studies published investigating the compatibility of DEBIRI with such a broad spectrum of contrast media. In our previous studies regarding DEBIRI, we used 6.5 mL of three different contrast media.⁹ After 24 h, the amount eluted was about 5% in admixtures with Imeron 300, 10% with Ultravist 300 and 10% with Accupaque 300. The elution of the drug loaded in the beads is determined by the ion-exchange mechanism and the diffusive-conductive transport of the drug from beads.^{8–10} Because irinotecan has no self-aggregation properties, the release rate depends on the ionic interactions with the sulfonate moieties of the beads only, and the elution is much faster than for doxorubicin and epirubicin. The differences in

rate and amount of irinotecan released after admixture of DEBIRI with contrast media are to be explained by different formulations, osmolalities and viscosities of the formulated contrast media (compare table 1). The storage temperature influences the release by higher diffusion coefficients and via the impact on viscosity of the solutions. High osmolality and low viscosity favour the elution of irinotecan. This explains the low amount of irinotecan eluted from loaded beads after admixture with Imeron 400 MCT and Accupaque 350. On the other hand, for Optiray 300, which features low osmolality and low viscosity, a rapid initial release and the highest amount of irinotecan released was detected. In accordance with the Stokes equation, high viscosity reduces the diffusion coefficient and the elution rate of irinotecan, which might be an argument for preferential use of high-viscosity contrast media in the TACE procedures.

Physicochemical stability of irinotecan-loaded DC BeadM1 was shown over a period of 28 days.⁹ Due to acidification (pH <3) of the test samples before running the HPLC assay, ring-open and ring-closed irinotecan are determined as a sum, and the influence of the pH of the contrast media on lactone-carboxylate equilibrium remains unknown. Of note, the pH values of the pure contrast media are very similar. Because it is already known that loading of irinotecan into the beads shifts the equilibrium between the active lactone and carboxylate in favour of the

Figure 3 Percentage rate (%) of irinotecan eluted from DEBIRI after mixing with 20 mL of six different non-ionic contrast media. Error bars indicate the relative SD.

Figure 4 Percentage rate (%) of irinotecan eluted from DEBIRI after mixing with 30 mL of seven different non-ionic contrast media. Error bars indicate the relative SD.

lactone form, the influence of the contrast medium on the pH-dependent equilibrium is most probably a subordinate one. Tang *et al*⁸ showed that the major fraction eluted was the lactone form when the beads were placed in phosphate buffered solution (PBS) with neutral pH. The half-life of the lactone form eluted into the PBS depends on the size of the beads, and suggests that the higher lactone fraction is favoured by sustained release from larger bead sizes.⁸ The high loading concentrations of the beads (50 mg/mL) also increase hydrophobicity of the loaded beads and retain the drug elution rate.¹⁰

No degradation products were detected, and the elution of irinotecan is testified as the only relevant incompatibility parameter. Moreover, during the assay validation tests, pure irinotecan drug solution was admixed with contrast medium, and the irinotecan content determined as a sum remained unchanged. However, the amount of irinotecan initially released was (except for Imeron 400 MCT) ≥ 5 mg, which corresponds to $\geq 5\%$ loss of irinotecan loaded when 30 mL of contrast media were admixed. Therefore, the admixtures are categorised as incompatible.

CONCLUSION

The amount of irinotecan released from loaded DC BeadM1 after admixture with seven different contrast media added up to

2.5% and maximum 17% of the loaded amount over the observation period, depending on the type and volume of contrast media used. Because of the rapid release (3%–9%) during the first 8 h, it is not recommendable to prepare the admixture of irinotecan-loaded beads with the bead size 70–150 μm with contrast medium in centralised cytotoxic preparation units in advance. Admixtures with contrast media should be performed with the smallest possible amounts by the radiologists immediately prior to the delivery procedure.

What this paper adds

What is already known on this subject?

- Mixtures of non-ionic contrast media and loaded microspheres are used for simultaneous chemoembolisation of liver tumours and metastases.
- Mixing of irinotecan-loaded beads (size $>100 \mu\text{m}$) with selected non-ionic contrast media rapidly decreases the loading efficiency of irinotecan by 5%–10%.

What is not yet known?

- Compatibility of the irinotecan-loaded DC BeadM1 (size 70–150 μm) with non-ionic contrast media is unknown.

What this study adds?

- Scientifically proven data about the rapid decrease of the loading efficiency of irinotecan-loaded DC BeadM1 (size 70–150 μm) after admixture with up to four volumes of seven different non-ionic contrast media.
- The recommendation not to prepare admixtures of irinotecan-loaded DC BeadM1 with contrast media in centralised cytotoxic preparation units in advance.

Table 1 Product characteristics of the non-ionic contrast media used (according to the summary of product characteristics)

Contrast medium	Active substance	pH value	Viscosity at 20°C (mPas)	Viscosity at 37°C (mPas)	Osmolality at 37°C Osm/kg H ₂ O
Accupaque 350	Iohexol	6.8–7.6	23.3	10.6	0.78
Imeron 400 MCT	Iomeprol	6.9–7.2	–	12.6 $\pm$ 1.1	0.726
Optiray 300	Ioversol	6.0–7.4	8.2 (25°C)	5.5	0.645
Optiray 350	Ioversol	6.0–7.4	14.3 (25°C)	9.0	0.78
Solutrast 370	Iopamidol	6.5–7.5	–	9.5	0.799
Ultravist 370	Iopromide	6.5–8.0	20.1	9.5	0.77
Xenetix 350	Iobitridol	7.3	21	10	0.915

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