Doxorubicin-Filled Radiopaque Microspheres for Improved Chemo-Embolization of Hepatocellular Carcinomas.

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Introduction. Hepatocellular carcinoma (HCC) is one of the deadliest malignancies worldwide.[1] The incidence of HCC is increasing, also in the western world.[2] Current treatment options include surgical resection, local ablative intervention or liver transplantation. Transarterial chemo-embolization (TACE) is a technique in which polymeric, drug-loaded particles are injected into the feeding artery of tumors (figure 1). The tumor is thus attacked in two ways: 1) by blocking arterial blood flow and 2) local release of anti-tumor drug.

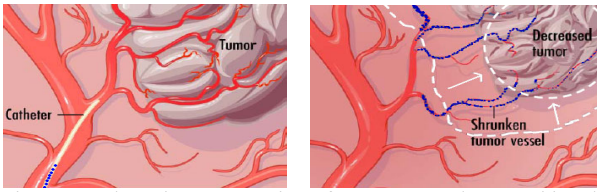

Figure 1. Schematic representation of TACE. A catheter positioned upstream the tumor, and microspheres are injected. The spheres block the feeding arteries and cause shrinkage of the tumor.

TACE is currently considered a palliative treatment for HCC patients, but there is room for improvement. Over the past decades great progress in this minimal invasive intervention has been achieved by improved imaging techniques and drug treatment protocols. However, the materials used for TACE are archaic and primitive in nature. Commercially available embolization microspheres are composed of poly(vinylalcohol) (Contour SE, Bead Block, DC beads) or tris-acryl-gelatin (Embosphere). These are solid, hydrophilic spheres that can be loaded with anti-tumor drugs like doxorubicin (DC Bead).[3] These embolization microspheres have several disadvantages: i) they are radiolucent, i.e. X-ray invisible, ii) they have limited drug-loading capacity, iii) they often suffer of premature release of drug (before and during the procedure). Here we present preliminary data on new engineered microspheres that do not have these shortcomings. Our microspheres can be easily detected with X-ray, demonstrate increased drug loading capacity and can be engineered to show controlled release profiles.

Methods. Microspheres with a diameter of 900 µm were prepared by suspension polymerization.[4] Radiopacity of the microspheres was caused by the incorporation of the iodine containing monomer 2-[4-iodobenzoyloxy]-ethyl methacrylate (4IEMA).[5] A hole with diameter 400 µm was made in the microspheres by laser ablation. This hole was used as drug reservoir. For filling, doxorubicin (Dox) was mixed with molten poly(caprolactone) (PCL) or poly(ethyleneglycol)(PEG) and inserted in the hole using a vacuum technique. Release of Dox was performed in buffer or serum. The released Dox was tested for bioactivity by incubation with fibroblasts and subsequent determination of cell viability.

Results. The synthesis of radiopaque, microspheres with drug cavities was successful. Holes were made in the microspheres as desired and filled with drug-polymer mixes (Figure 2). Radiopacity of the microspheres was confirmed by X-ray fluorimetry.

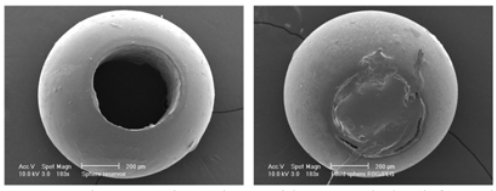

Figure 2. SEM images microsphere with empty hole (left) and filled with doxorucin (right).

The Dox release-profile was dependent on the medium in which the experiment was performed. Release in serum was faster than when determined in buffer. Dox mixed with PCL showed a slower release than Dox mixed with PEG. Finally the fast initial burst release could be prevented by covering the hole of the spheres with a protective layer that dissolved at 35 ºC

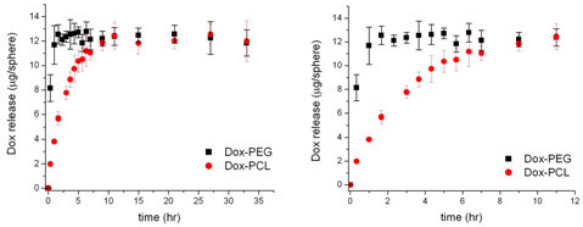

Figure 3. Dox release for 3 days (left) an 12 hours (right) from microspheres filled with Dox-PCL or Dox-PEG.

Release of Dox was complete within 24 hours. Since Dox has limited (thermo)stability, longer release profiles are probably not effective. The capacity for Dox was increased at least 2- to 3-fold, compared to the published data for the commercially available Dox containing DC beads.[6]

Conclusions. Radiopaque microspheres with a drug-filled cavity may be a promising alternative to Dox-soaked PVA microspheres. Our novel microspheres have increased drug-loading capacity. Additionally, the release kinetics can be tuned by addition of a suitable polymer, which regulates Dox-release. The next step will be to assess the performance of these microspheres concerning injectability and in vivo drug release.

References.

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