Drug Eluting Beads vs. Lipiodol-based Emulsion regarding Local Drug Release and Effect in Patients with Hepatocellular Carcinoma – Interim Analysis of a Clinical Trial –

E. Lilienberg\textsuperscript{1}, I.R. Dubbelboer\textsuperscript{1}, A. Karalli\textsuperscript{2}, P. Stål\textsuperscript{2}, C. Ebeling Barbier\textsuperscript{3}, A. Norén\textsuperscript{3}, F. Duraj\textsuperscript{3}, R. Nyman\textsuperscript{3}, E. Sjögren\textsuperscript{1}, and H. Lennernäs\textsuperscript{1}

\textsuperscript{1}Department of Pharmacy, Uppsala University, 751 23 Uppsala, Sweden; \textsuperscript{2}Karolinska University Hospital, 141 86 Stockholm, Sweden; \textsuperscript{3}Uppsala University Hospital, 751 85 Uppsala, Sweden
elsa.lilienberg@farmaci.uu.se

ABSTRACT SUMMARY

An open, non-randomized and prospective multi-center study was designed to investigate the in vivo drug release from two drug delivery systems used in the palliative treatment of hepatocellular carcinoma (HCC). Results from local blood data were not concordant with the systemic pharmacokinetic profile and was shown to be useful when investigating in vivo release from regional drug delivery systems. Magnetic resonance imaging before and after the treatment showed tumor necrosis in both study arms.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary liver cancer that is the 6\textsuperscript{th} most common and the 2\textsuperscript{nd} most lethal cancer-form worldwide \cite{1}. The recommended palliative treatment for unresectable HCC is transarterial chemo-embolization (TACE). The TACE-technique (Fig. 1) is used because it intends to: i) deliver cytostatic drug locally close to the tumor and ii) embolize the tumor feeding vessels in order to starve the tumor on nutrition. TACE can be performed because HCC is provided with blood mainly from the hepatic artery, while normal liver tissue s supplied by 2/3 from the portal vein.

Two drug delivery systems specific for TACE are in clinical use in Sweden, and most often with the chemotherapeutic drug doxorubicin. These drug delivery systems are i) water-in-oil emulsion based aqueous doxorubicin in the oily contrast agent lipiodol (LIPDOX) where release is dependent on its stability and drug diffusion, and ii) drug eluting beads (DC Bead\textsuperscript{TM}) which is microparticle beads loaded with doxorubicin (DCBDOX) where the loading and release depend on an ion-exchange mechanism with doxorubicin \cite{2}. DCBDOX are known to cause reduced frequency and severity of drug-related side-effects than LIPDOX \cite{3}. However, it is not yet established which of these drug delivery systems that provides the most optimal release profile and anti-tumor effect. In a healthy pig model, LIPDOX generates higher availability of doxorubicin both locally and systemically compared to DCBDOX \cite{4}, but there is still a gap in the understanding about if the tumor micro-environment affects the drug release and local disposition.

The primary aim with this study is to compare the two drug delivery systems, LIPDOX and DCBDOX, in patients with HCC. The comparison will be based on the local and systemic distribution of doxorubicin and its primary metabolite doxorubicinol, and also an evaluation of the tumor size reduction following one treatment. The approach to investigate relevant processes locally in patient will provide novel data that will improve pharmaceutical development of regional drug delivery systems.

Figure 1. An illustration of the transarterial chemo-embolization technique (TACE), where the drug is locally administered via the hepatic artery. Special for this study is the addition of a vena caval catheter in height with the hepatic veins, in order to collect local blood samples.

EXPERIMENTAL METHODS

Today, twelve of 28 HCC patients have been enrolled in this open, non-randomized and prospective multi-center study. All patients provided written informed consent. The study protocol was
approved by the regional ethical review board in Uppsala Dnr 2013/227 and registered in the European Clinical Trials Database (EudraCTnr 2013-001244-56).

Six patients received treatment with LIPDOX, and six patients received DCBDOX via the TACE-technique (Fig. 1). Additional to the hepatic artery catheter that was inserted to deliver the drug delivery systems, a catheter was inserted in the superior caval vein (in height with the hepatic veins), by an experienced interventional radiologist.

Thereafter local blood samples were collected at specific time points up to 6 h after TACE and systemic blood samples were collected from peripheral veins up to 7 days after TACE. Plasma was analyzed, for doxorubicin and doxorubicinol, with UPLC-MS.

Before and after the TACE treatment, the patients received an examination with magnetic resonance (MR) imaging to investigate the effect of the treatment on the tumor.

RESULTS AND DISCUSSION

The demographics of the included patients are summarized in Table 1.

<table>
<thead>
<tr>
<th>Treatment used</th>
<th>Lipiodol-based emulsion (LIPDOX)</th>
<th>Drug eluting beads (DCBDOX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Age</td>
<td>69 (55-83)</td>
<td>68 (53-81)</td>
</tr>
<tr>
<td>Sex</td>
<td>4 M/2 F</td>
<td>3 M/3 F</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87 (70-97)</td>
<td>82 (61-110)</td>
</tr>
<tr>
<td>Etiology of HCC</td>
<td>1/1/4</td>
<td>3/1/2</td>
</tr>
<tr>
<td>(Hepatitis B or C virus/alcohol/other)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of tumors (1/1+satellites/2/3+)</td>
<td>3/1/1/1</td>
<td>4/0/2/0</td>
</tr>
<tr>
<td>Tumor size of treated tumor before TACE (ø cm)</td>
<td>6.8 (4.5-10)</td>
<td>3.9 (0.8-6.4)</td>
</tr>
</tbody>
</table>

Data are presented as mean (range).

Results from blood data sampled over time indicated that the systemic pharmacokinetic profile is not concordant with the local pharmacokinetic profile (i.e drug release from the delivery system). It reveals that doxorubicin has a local extended release from both LIPDOX and DCBDOX, however, much slower for DCBDOX. Less DOX reached the systemic blood circulation from DCBDOX than for LIPDOX (p<0.05). This finding is supported by previous reports where the in vivo release was slower from DCBDOX (3, 4).

MR imaging showed a clear circulatory effect of the tumor after the treatment for both LIPDOX and DCBDOX (Fig. 2), which is interpreted as tumor necrosis. However, more patients need to be included to be able to compare difference in tumor size reduction between LIPDOX and DCBDOX and to be able to perform statistical analysis of the blood data.

CONCLUSION

Local blood sampling was useful when investigating release from regional drug delivery systems. LIPDOX had a faster in vivo release than DCBDOX and doxorubicin reached the circulation in a higher degree.

MR imaging before and after TACE showed tumor necrosis both after DCBDOX and LIPDOX. More patients need to be included for statistical analysis of data.

REFERENCES