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Safety Profile and Efficacy of Chemoembolization with Doxorubicin - Loaded Polyethylene Glycol Microspheres in Patients with Hepatocellular Carcinoma

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AIM: This study was designed as a preliminary investigation of safety and efficacy of LifePearl, polyethylene glycol microspheres loaded with doxorubicin for treatment of locally untreatable (i.e., unresectable and not suitable for local thermal ablation) hepatocellular carcinoma (HCC).

MATERIAL AND METHODS: Patients with locally untreatable HCC (mono- or bilobar disease, ECOG performance status 0-1, Chilg-Pugh score < 11) were analysed for this single arm Unicenter retrospective study. All the information were acquired through our local hospital information system. DEB-TACE was performed with 100-200 microns LifePearl loaded with 75-150 mg of doxorubicin depending on tumour size. One interventional radiologist with experience of more than 350 TACE procedures and one fellow in radiology performed all embolisations.

RESULTS: Twenty subjects with 29 tumours were treated (mean age 66.2 years). Child-Pugh status was A for 12 pts. (60%), B for 6 pts. (30%) and C for 2 pts. (10%). Three patients had insignificant ascites. Most patients (70%) underwent < 3 DEB-TACE procedures. Average doxorubicin dose was 71.1 mg per procedure. One patient had procedure-related SAE (acute pancreatitis) within the postembolization period which was induced due to non-target embolisation of the superior pancreaticoduodenal artery. Six-month freedom from procedure-related SAE or death was 95% (one necrotizing pancreatitis). Tumor response or stable disease was achieved in 95% (19/20) of subjects. Freedom from tumor progression or death at 6 months was 95%. One-year survival rate was 90% overall.

CONCLUSION: The results from this investigation suggest that LifePearl microspheres, Terumo loaded with doxorubicin can provide an excellent local tumour control with very few side effects in a relatively homogeneous group of patients with locally untreatable HCC.

Abstract

Introduction

Patients with locally untreatable HCC (i.e., unresectable and not suitable for local thermal ablation) have few treatment options [1]. Systemic chemotherapy with sorafenib has shown to modestly prolong survival in patients with advanced stage disease [1], [2] and transarterial chemoembolization (TACE) is recommended for patients in intermediate stage disease [1]. Meta-analyses have shown that TACE performed with doxorubicin-loaded beads has similar efficacy but fewer side effects than conventional lipiodol-based TACE [3], [4]. So far there are four types of drug-eluting microspheres on the market. The first three types are based on polyvinyl alcohol (PVA) and the last one developed are LifePearl made from polyethylene glycol. In our centre, we started using this polyethylene glycol platform since 2016. So far, there are only a couple of preliminary studies in the literature, regarding the safety profile of polyethylene glycol particles.

This investigation was designed in a retrospective fashion to evaluate safety and efficacy of LifePearl microspheres loaded with doxorubicin for DEB-TACE treatment of locally untreatable hepatocellular carcinoma, specifically the size of 100 and 200 microns and 75-150 mg of doxorubicin.

Material and Methods

Study design

This investigation represents a retrospective, Unicenter, single-arm feasibility study of chemoembolization with 100 and 200 microns doxorubicin-loaded LifePearl microparticles for treatment of locally unresectable HCC.

Study Patients

Patients eligible for the study were adults with a confirmed diagnosis of HCC according to the European Association of Study of the Liver (EASL) criteria [6] and were staged according to BCLC criteria [1]. Eastern Cooperative Oncology Group (ECOG) [7] performance status was 0 and 1, and we included patients with Child-Pugh score of < 11 points (i.e. A, B or C 10) [8]. Twenty patients with 29 tumours were enrolled. Tumor size ranged between 1.5-15 cm in largest diameter (mean diameter = 5.67 cm) both mono or bilobar disease. Lack of main portal vein trunk or common bile duct invasion was confirmed with preprocedural multidetector computed tomography (MDCT). Patients had laboratory values in the following ranges: white blood cell count > 3500/ml, absolute neutrophil count > 1500 cells/ml, INR < 1.8, partial thromboplastin time < 38 s, platelet number > 5 x 10^4 ml, blood bilirubin level < 20 mmol/L, aspartate aminotransferase (AST) level and alanine aminotransferase (ALT) within five times of normal range of each organ, serum creatinine level < 2.5 mg/dL, hemoglobin > 8.0 g/dL, and alkaline phosphatase < 630 IU/L.

Embolisation Procedure

LifePearl microspheres are polyethylene glycol particles that can be loaded with anthracyclines such as doxorubicin, epirubicin, idarubicin or other chemotherapeutic drugs, such as irinotecan [5], [9], [10], [11]. Patients in this study were treated with 100 and 200 microns diameter LifePearl microspheres, which are calibrated to ± 25 microns. One 2 ml syringe of microspheres can be loaded with up to 75 mg of doxorubicin, with little shrinkage observed after drug loading [9]. Doxorubicin loading was performed according to the manufacturer's instructions. A procedural doxorubicin dose of 75 mg/m^2 body surface area was targeted. A minimum of two treatments per lesion, separated by 4 weeks interval were performed. Thus, patients with bilobar disease were treated with at least 4 sessions (two per liver lobe).

Chemoembolization procedures were performed with antibiotic prophylaxis, analgesic and antiemetic medication at the physician's discretion. Angiography of the hepatic and mesenteric arteries was performed before chemoembolization to confirm anatomical eligibility and identify tumour feeder arteries. Hepatic segmental or subsegmental arteries supplying the lesion were selectively catheterised with microcatheter while ensuring sufficient flow to the tumour, and a mixture of 100 or 200 microns of doxorubicin-loaded microspheres and non-ionic contrast agent was slowly injected. Bland microspheres were also used in some cases if blood stasis was not achieved after the delivery of the desired drug dose.

Safety and efficacy endpoints

Safety was observed as freedom from severe adverse events (SAE) at 30 days and 6 months, and efficacy as freedom from tumour progression at 6 months after chemoembolization. Secondary points were the rate of local tumour control and 12-month survival.

Adverse event monitoring was observed and recorded during the treatment and follow-up phases. Tumour imaging (contrast-enhanced CT) was performed, and measurements were taken within 4 weeks before the first DEB-TACE procedure (baseline) and 4 weeks following every embolisation procedure. Repeat DEB-TACE procedures were performed when follow-up imaging studies showed residual enhancement until complete response according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria was achieved. Imaging was repeated at 4 to 6 weeks intervals to determine the need for additional DEB-TACE procedures and was scheduled to be performed 3 and 6 months following the last DEB-TACE procedure and 12 months from the initial treatment. Clinical and laboratory assessments were also repeated at each of these visits. Tumour response was assessed based on mRECIST criteria [12]. "Best overall response" was defined as the smallest measurement of hypervascularized tumour tissue recorded from the start of treatment until disease progression/ recurrence. Images were evaluated by the interventional radiologist who performed the DEB-TACE procedures.

Results

From February 2016 to July 2018, 20 patients with 29 tumours were treated at our department for interventional radiology. Patient and lesion characteristics are summarized in Table 1. There was no statistically significant difference among patient groups regarding the aetiology of cirrhosis ($p > 0.05$). ECOG performance status of 0 is significantly more included than ECOG 1 ($p < 0.05$).

Table 1: Baseline patient characteristics

Characteristic	N (%) (*N = 20*)	P
Sex (male/female)	15/5	P = 0.0016
Age, years (median, range)	66.2 (55-80)	
Aetiology of cirrhosis		
Alcohol abuse	5 (25.0)	
Hepatitis B	7 (35.0)	P > 0.05
Hepatitis C	0 (0)	
Unknown/other	8 (40.0)	
Child-Pugh classification		
A	10 (50.0)	
B	8 (40.0)	P = 0.0058
C	2 (10.0)	P = 0.0258
ECOG performance status		
0	16 (80.0)	P = 0.0001
1	4 (20.0)	
BCLC classification		
A	12 (60.0)	P = 0.0009
B	6 (30.0	
C	2 (10.0)	
Prior liver surgery	1 (5.0)	
Prior RFA therapy	1 (5.0)	
Liver lobes involved		
1 (Monolobar HCC)	17 (85.0)	P = 0.0000
2 (Bilobar HCC)	3 (15.0)	
Tumor size (largest diameter; *N = 29*)		
< 3 cm	10 (34.5)	
3 ≤ 5 cm	5 (17.2)	P > 0.05
5 ≤ 10 cm	9 (31.0)	
> 10 cm	5 (17.2)	
Range	1-15 cm	

Most of the patients (85%) had monolobar disease (P value < 0.05) and 90% had early or intermediate stage HCC, BCLC A and B, significantly more than C (P < 0.05). Only two patients had prior therapy (surgery or radiofrequency ablation) before chemoembolization; none had systemic chemotherapy.

All patients that were included in the study underwent at least two successful DEB-TACE procedures, except one patient who had one chemoembolization only because we were confident that we achieved a complete response after the first TACE which was confirmed with several consecutive imaging controls.

Safety

By 30 days from their first embolisation procedure with drug-loaded microspheres, 95% (*n* = 19) of patients remained free from procedure-related severe adverse events. One patient (5%) experienced acute pancreatitis which was confirmed by clinical signs, laboratory tests and imaging studies. After carefully reviewing the DEB-TACE procedure in this patient we realised that it was due to reflux of drug-loaded microparticles in the superior panreatoduodenal artery because tumor was supplied from the gastroduodenal artery and partially from the right hepatic artery. The patient had a history of cirrhosis of the liver, previous liver surgery due to HCC, Hepatitis B infection, portal hypertension, chronic erosive gastritis and presented with BCLC B HCC. This complication was treated with conservative medical treatment and prolonged hospitalisation. The patient recovered and was discharged from hospital 10 days later. Prolonged postembolization syndrome occurred in 6 patients, followed by moderate abdominal pain, slightly elevated temperature, nausea/vomiting and loss of appetite. These patients remained in the hospital for 3 nights and then were discharged in good clinical condition. The occurrence of post-embolisation syndrome symptoms after embolisation procedures is summarised in Table 2. Post-embolization syndrome events were grade 1 or 2.

Table 2: Occurrence of post-embolisation syndrome following DEB-TACE procedures

	1st DEB-TACE (*N* = 20)	2nd DEB-TACE (*N* = 19)	3rd DEB-TACE (*N* = 10)	4th DEB-TACE (*N* = 3)	5th DEB-TACE (*N* = 2)
Postembolization syndrome, n (%)	11 (55.0)	8 (42.1)	7 (70.0)	2 (66.6)	1 (50.0)
Abdominal pain	7 (35.0)	4 (21.0)	6 (60.0)	1 (33.3)	0 (0)
Nausea/vomiting	1 (5.0)	2 (10.5)	1 (10.0)	1 (33.3)	0 (0)
Fever	1 (5.0)	2 (10.5)	3 (30.0)	0 (0)	1 (50.0)

According to the index of dynamics, a decrease in postembolization syndrome is registered from first to third DEB-TACE for 36.4%, and first to fifth DEB-TACE for 90.9%.

By 6 months from their first DEB-TACE procedure, 95% (N = 19) of patients were free from procedure-related serious adverse events or death. All patients survived at least 6 months after treatment.

Imaging to evaluate tumour response was available for all 20 patients. According to mRECIST criteria for best response, complete response was achieved in 10 patients (50%), partial response in 6 (30%), stable disease in 3 (15%) and progressive disease in 1 (5%). Significantly more patients had complete response versus stable and progressive disease (P = 0.0181 and P = 0.0014). At 6 months, 95% of patients were free from tumour progression or death. The one patient who had tumour progression had three embolisation procedures before progression was observed. At 6 months, 95% of patients were free from tumour progression or death. The one patient who had tumour progression had three embolisation procedures before progression was observed.

One-year survival rate was 90% (18/20). One death was due to other comorbidities, not tumour itself, the other one was due to progressive HCC disease. Both of these patients were staged as BCLC C disease before treatment.

Discussion

The results from this study demonstrate a high rate of local tumour control and only one severe adverse event among patients treated with doxorubicin-loaded PEG microspheres. In a preliminary single-center retrospective study by Veloso Gomez et al., [21] in 302 patients with HCC, treated with polyethene glycol microspheres, more than 80% of patients had objective tumour response

and the one-year survival rate was 93.5%. However, in this study, a large number of patients (142) had Barcelona Clinic Liver Cancer stage A disease and 134 had BCLC stage B disease which is a good prognostic factor for HCC patients. Also, mean index tumour size in this study was 3.7 cm, and in our study median tumour diameter was 5.7 cm. The incidence of serious adverse events or Grade 3-4 toxicities following doxorubicin-eluting embolic therapy for HCC has generally been low in previous studies [13], [14], [15] and was comparably low in our investigation. For example, Prajapati et al., [13] reported an overall adverse event rate of 30% within 30 days of embolisation, with the majority of complications Grade 1-2 and no Grade 4 toxicities in a retrospective study od 121 patients. In a randomised study, approximately 24% of 93 patients treated with drug-eluting embolic agent reported serious adverse events within 30 days, and two patients died [14]. In this study, no deaths or systemic toxicities occurred within 30 days, and only 1 patient had procedure-related serious adverse event. Although the heterogeneous nature of HCC patients characteristics, variable treatment regimes, and evaluation criteria across studies limit comparisons between studies, results from previous studies of doxorubicin-loaded microspheres treatment of HCC provide background for the findings observed in our investigation.

Post-embolization syndrome, or symptoms like abdominal pain, nausea, vomiting, and fever has been reported in 5-100% of patients in previous studies [5], [13], [14], [15], [16], [17]. Richter et al. reported tumour response rate with complete or partial tumour response observed in 67% of patients in MIRACLE I study [20]. In our study, we found that 80% of the patients had a complete or partial response to intraarterial therapy and only 1 patient (5%) displayed tumour progression during follow up. The one-year survival rate in MIRACLE I study was 56% with a greater rate among patients with Child-Pugh A liver cirrhosis (75%) [20]. In our study, one-year survival rate was 90%, but compared to the patients in MIRACLE I, in our study Child-Pugh A and B cirrhosis was found in 90% of patients. We had 2 patients with no significant ascites while in MIRACLE I, 10 patients had severe ascites. Previously reported one-year survival rates among different studies varied between 58 and 92% [5], [15], [18], with stratifying factors such as the presence of ascites and Child-Pugh classification of B or C associated with poorer survival [13], [18], [19]. The proportion of patients with ascites or liver function with Child-Pugh B and C are relatively low in our group of patients but not very different than other studies (i.e., no patients with ascites or Child-Pugh C were included in the studies from Reyes et al., [15] or Malagari et al., [5].

The limitations of this study are that it is a retrospective one and that the sample size is relatively small. Study sample is with relatively homogeneous clinical characteristics. The results from this investigation suggest that LifePearl polyethylene glycol microspheres, when loaded with doxorubicin, can provide excellent local tumour control with a very low rate of procedure-related complications in a well-selected group of patients with locally untreatable HCC.

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