Research Article

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Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design

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Background & Aims: Transarterial chemoembolisation (TACE) improves survival of properly selected patients with hepatocellular carcinoma (HCC). Drug eluting beads (DEB) provide a calibrated and homogenous procedure while increasing efficacy. Outcome data applying this technology is lacking, and this is instrumental for clinical decision-making and for trial design.

We evaluated the survival of HCC patients treated with DEB-TACE following a strict selection (preserved liver function, absence of symptoms, extrahepatic spread or vascular invasion).

Methods: We registered baseline characteristics, the development of treatment-related adverse events, and the overall survival of all HCC patients treated by DEB-TACE from February 2004 to June 2010.

Results: One hundred and four patients were treated with DEB-TACE. All but one were cirrhotic, 62.5% HCV+, 95% Child-Pugh A, 41 BCLC-A and 63 BCLC-B. Causes of DEB-TACE treatment in BCLC-A patients were: 35 unfeasible ablation, and six post-treatment recurrences. After a median follow-up of 24.5 months, 38 patients had died, two patients had received transplantation and 24 had received sorafenib because of untreatable tumour progression. Median survival of the cohort was 48.6 months (95% CI: 36.9–61.2), while it was 54.2 months in BCLC stage A and 47.7 months in stage B. Median survival after censoring follow-up at time of transplant/sorafenib was 47.7 (95% CI: 37.9–57.5) months.

Conclusions: These data validate the safety of DEB-TACE and show that the survival expectancy applying current selection criteria and technique is better than that previously reported. A 50% survival at 4 years should be considered when suggesting treatment for patients fitting into controversial scenarios such as expanded criteria for transplantation/resection for multifocal HCC.

Keywords: Hepatocellular carcinoma; Chemoembolization; Drug eluting beads (DEB); Safety; Survival.

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Introduction

Transarterial chemoembolisation (TACE) is an established treatment for patients diagnosed with hepatocellular carcinoma (HCC) [1]. Optimal candidates for it are asymptomatic patients with compensated liver disease without extrahepatic spread or vascular invasion. This defines the BCLC-B stage, but TACE is also applied to patients at an earlier stage (BCLC-A) who are not considered for surgery or ablation. This clinical situation is known as "treatment stage migration" and indicates that each BCLC stage has each first line option. However, according to the individual patient's profiling, the treatment selection is tailored for each patient. Until recently, TACE has been performed using lipiodol intra-arterial chemotherapy followed by embolisation with Gelfoam particles ('conventional TACE'). This was the technique used in most TACE trials that established this treatment as standard. The limitations of the technique are well known. Gelfoam was prepared manually, arterial obstruction could be heterogeneous and it lasted less than 72 h. In addition, the time between chemotherapy injection and vessel obstruction allowed chemotherapy to be released to the systemic circulation and induced toxicity that impaired the tolerance of the patients. The development of Drug-Eluting Beads (DEB) represents a major advancement. DEB are formed by non-resorbable hydrogel and are loaded with the chemotherapy drug (doxorubicin). This is slowly released upon injection into the blood stream and systemic passage is significantly reduced despite injection of higher doses of chemotherapy. As a consequence, the treatment efficacy and tolerance are improved [2–5] as compared to conventional TACE [6,7].

The refinement in treatment application has overlapped in time with the improvement of the criteria to select candidates [8]. Most groups do not treat patients with decompensated liver disease and it is acknowledged that the presence of vascular invasion (even segmental) impairs tolerance and outcome [9,10]. As a consequence, the survival data (median survival below 2 years)

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reported one decade ago are no longer valid [6,7,11]. This prompted the current retrospective study that reports the survival of HCC patients treated with DEB-TACE in our group.

Patients and methods

Patient evaluation

The study population consisted of those patients treated with DEB-TACE at our institution between February 2004 and June 2010, and was followed-up until June 2011. After our phase II trial by Varela *et al.* [2] showing the safety and chemotherapy pharmacokinetics of DEB-TACE, we had to wait for confirmatory studies to have the new material reimbursed for clinical practice. Because of this need, the cohort includes the 22 patients recruited in the Varela *et al.* study who did not receive TACE with Gelfoam during follow-up and 82 additional patients that were treated upon getting the allowance to use DEB. Patients treated by conventional TACE were excluded.

The inclusion criteria for DEB-TACE were: (1) HCC diagnosed by pathology or by non-invasive criteria according to AASLD guidelines [1,12], (2) patients with early stage HCC [13] that were not candidates for resection, transplantation, ablation or had failed/recurred after resection/ablation or (3) intermediate HCC patients following the BCLC staging system, (4) normal liver or compensated cirrhosis with preserved liver function (Child-Pugh score $\leqslant$7 points) [14], (5) performance status 0 [15], (6) adequate clotting profile (platelet count $\geqslant 60 \times 10^9$/L, haemoglobin >8.5 g/dl, and prothrombin time >50%), (7) adequate hepatic function (albumin >2.8 g/dl, bilirubin <3 mg/dl and alanine and aspartate aminotransferase <5 times the upper limit of the normal range), (8) adequate renal function (serum creatinine <1.5 times the upper limit of the normal range).

Exclusion criteria were: (1) portal vein thrombosis (even segmental) or hepatofugal blood flow, (2) impaired hepatic function, (3) contraindication for arterial endovascular procedure, (4) contraindication for the administration of doxorubicin.

Treatment

All patients received at least one session of DEB-TACE (DC Beads®, Biocompatibles, UK Ltd.). All tumour sites were treated in a single session even if they affected both lobes. Treatment efficacy was assessed at one month. If complete response or tumour necrosis was >90% (defined by the absence of contrast uptake in the arterial phase at dynamic imaging) retreatment was considered every 6 months. Because of the non-inclusion in a prospective study, some patients have had their follow-up imaging done in their referring centre.

DEB-TACE sessions were repeated until occurrence of symptomatic progression, extrahepatic spread or vascular invasion, development of liver failure or appearance of severe adverse events [16] . Hence, tumour progression was not taken as treatment failure and DEB-TACE was repeated if contraindications had not appeared. When progression was not treatable by DEB-TACE [16], the patients were evaluated for second line options that, upon sorafenib proof of efficacy, have had this agent as the first choice.

No antibiotic prophylaxis [17,18] or anti-inflammatory drugs were administered prior to treatment. Pain during the procedure was managed individually. Pain and fever attributed to postembolisation syndrome were controlled individually.

Angiographic technique

The procedure was conducted using the equipment Axiom Artis (Siemens, Germany). Diagnostic visceral angiography of the celiac trunk and superior mesenteric artery was first performed to determine the arterial supply to the liver, the variant arterial anatomy, and the patency of the portal vein. The gastroduodenal, cystic, and gastric arteries were carefully noted to avoid the backward flow of chemoembolisation material to these arteries. Selective angiography of the common hepatic artery was then carried out to evaluate tumoural vessels. The multiplanar and maximum intensity projection reconstructions of the 1-mm images obtained from the multiphasic CT scan added some information on the tumoural feeders.

The end point of treatment was to achieve complete tumour devascularisation. Chemoembolisation of all tumoural vessels was performed as distally as possible in one single session. Therefore, we first intended to treat from the tumour feeder, and if this was not feasible or not enough to ensure complete treatment, we continued from subsegmental or segmental arteries. Patients with unifocal lesions were treated selectively from the tumour feeders. Patients with multiple lesions were treated with embolisation from multiple segmental and/or subsegmental arteries. For this purpose, we always used a coaxial microcatheter 2.7F (Progreat, Terumo Europe, Leuven) and in specific cases a coaxial 2.4F microcatheter (Excelsior, Boston Scientific, Boston, Massachussets). For cases where suprasselective catheterisation was difficult, a 0.014″ microguidewire (Syncro; Boston Scientific, Boston, Massachussets) was used. DEB were loaded at the hospital pharmacy 12 h before use. Loaded beads were mixed with iodinate contrast in a proportion 1:1 (5 ml of DC Beads in 5 ml of contrast), 5–10 min before injection. During the administration, we added contrast or saline depending on the concentration of beads and fluid density. We used 3-ml injection syringes. Beads were administered under continuous fluoroscopic monitoring until stagnation of flow was achieved. Maximum dose administered was 150 mg of doxorubicin (two vials); dose was not tailored according to body surface or weight. The size of beads used in the Varela *et al.* study was 500–700 microns [2] in order to assess safety and minimise the risk of biliary damage by using smaller beads. Upon establishing safety when using smaller beads by other authors, we used 300–500 microns in the remaining patients. These are preferred as the potential microcatheter clogging is almost completely avoided. If stagnation of flow was not achieved after the injection of two DEB vials, we continued injecting non-loaded spherical particles of 300–500 microns (BeadBlock). A final angiography to confirm complete tumour devascularisation was performed in all cases.

Clinical and radiological follow-up

Baseline clinical examination, and laboratory and tumour evaluation were performed in all patients. Follow-up included clinical examination, laboratory data, tumour evaluation, and registration of serious adverse events following version 3.0 Terminology Criteria for Adverse Events (CTCAE), which determines hospitalisation.

The usual policy in patients at the BCLC is to perform follow-up imaging with a multiphasic study (non-enhanced, arterial, portal and late venous phases) using either an helical CT or a 64-row multidetector CT scanner with 120 ml of non-ionic contrast agent at a rate of 4 ml/s. Images are reconstructed at 4-mm thickness in axial and coronal planes. This protocol is recommended when patients are not followed at the BCLC, but because of the non-prospective collection of the data with adequate monitoring, it is not possible to ensure that timing and technology are homogeneous in the whole cohort. Accordingly, assessment of response rate and time to progression has not been evaluated and we only focused on survival. This is a robust end point in terms of validation and registration in any time-to-event analysis.

Same limitation applies to untreatable progression that is defined as development of HCC progression not amenable for DEB-TACE because of limiting technical issues, significant disseminated intrahepatic disease, vascular invasion or extrahepatic spread, clinical intolerance to TACE and/or development of liver failure [16].

Statistical analysis

Quantitative variables were expressed as median and range and categorically as count and proportions. Patients were classified according to BCLC staging. Differences between subgroups were evaluated by the Chi-squared test or Fisher's exact test for categorical variables and by Student t test or non-parametric U-Mann–Whitney test for quantitative variables. Prognostic power of clinical and biochemical profile was assessed by dividing parameters according to the median of each parameters. Univariate analysis was performed on each clinical and biochemistry variable to examine their influence on patient's survival. Survival rates and curves were determined using the Kaplan–Meier method, and compared using the log rank test. A conventional p value less than 0.05 was considered significant. Last date for data collection was June 23, 2011. Analysis was done without any censoring and also censoring survival at the time of liver transplantation or sorafenib treatment. This would rule out the impact of these treatments on the observed survival.

All calculations were done with SPSS package version 18 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics of patients

Between February 2004 and June 2010, 274 patients received treatment with TACE. A total of 104 patients met the inclusion criteria and are the subject of this study. The excluded patients had received at least one conventional TACE. The baseline charac-