Transarterial Hepatic Chemoembolization with 70–150 μm Drug-Eluting Beads: Assessment of Clinical Safety and Liver Toxicity Profile

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ABSTRACT

Purpose: To assess the incidence and severity of adverse events (AEs) in the form of clinical symptoms and liver/biliary injuries (LBI) in patients with hepatic malignancies treated with transarterial chemoembolization using 70–150 μm drug-eluting beads (DEBs).

Materials and Methods: A single-institution retrospective analysis was performed in 37 patients (25 patients with hepatocellular carcinoma and 12 patients with metastatic disease) who underwent 43 sessions of segmental/subsegmental 70–150 μm DEB transarterial chemoembolization with doxorubicin (38 sessions) or irinotecan (5 sessions). Patient inclusion criteria included the presence of the following lesion features: small diameter ($\leq$ 3 cm), hypovascular, or with areas of residual disease after other locoregional therapies. Mean tumor diameter was 3.4 cm. Mean imaging and clinical follow-up periods were 171 days and 373 days, respectively. Clinical, laboratory, and imaging data were used to identify and classify clinically symptomatic AEs per session and LBI per patient according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Predictors for the occurrence of LBI were evaluated by logistic regression analysis.

Results: No grade 4 or 5 AEs were recorded. Clinically symptomatic AEs occurred in 29 (67.4%) sessions (grade 1–2, 28 sessions; grade 3, 1 session), all constituting postembolization syndrome. Asymptomatic LBI occurred in 11 (29.7%) patients (grade 1, 8 patients; grade 2, 3 patients). The mean time between 70–150 μm DEB transarterial chemoembolization session and appearance of LBI was 71 days (range, 21–223 d). No predictive factors for the development of LBI were identified.

Conclusions: Transarterial chemoembolization with 70–150 μm DEBs was considered safe in the present study population given the acceptably low incidence and severity of AEs.

ABBREVIATIONS

AE = adverse event, DEB = drug-eluting bead, HCC = hepatocellular carcinoma, LBI = liver/biliary injuries, PES = postembolization syndrome

The existing literature on the use of drug-eluting particles (drug-eluting beads [DEBs]) for transarterial chemoembolization has described several advantages, including better patient tolerability; deeper penetration of DEBs into the tumor vasculature; sustained, time-released delivery of chemotherapy into the tumor; and a significant reduction in the systemic passage of the chemotherapeutic agent (1,2). Despite the reported benefits, fundamental questions remain with respect to optimal particle size and type and chemotherapeutic dose for clinical use (3,4). Existing data regarding the use of particles sized 100–300 μm, 300–500 μm, and 500–700 μm show adverse event (AE) rates ranging from 10% to 58%, with fewer AEs occurring with the use of smaller

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particles (4–6). The introduction of a new class of DEBs with a nominal bead size of 70–150 μm (LC/DC Bead[M1]; Biocompatibles UK Ltd, Farnham, Surrey, United Kingdom) has increased the options for therapeutic drug delivery and raised the issue of how these smallest DEBs can be best incorporated into clinical practice.

In animal models, 70–150 μm DEBs permit deeper and more homogeneous vessel penetration with improved drug coverage compared with 100–300 μm DEBs (7). Nevertheless, serious and fatal complications, such as hepatic failure resulting from nontumoral tissue damage by capillary bed saturation and pulmonary complications resulting from nontarget embolization through the hepatic microcirculation into the systemic vasculature, have been reported with the use of small-sized particles in patients undergoing either bland embolization or transarterial chemoembolization (8,9). The development of liver/biliary injuries (LBI) is a common finding after transarterial chemoembolization secondary to ischemia caused by the saturation of the peribiliary arterial plexus with chemoembolic material leading to bile duct necrosis, followed by stricture and subsequent biliary dilatation and biloma formation. Additionally, the inherent pharmacokinetics profile of the DEBs exposes the nontumoral surrounding liver to a high concentration of cytotoxic agents (10–12), making it an independent risk factor for the development of LBI (13,14). With regard to the incidence of LBI in patients treated with DEBs, the available literature shows a lower incidence of LBI occurring with small (< 300 μm) particles compared with larger (> 300 μm) ones (6). At the present time, no information is available regarding the incidence and clinical significance of LBI with the use of 70–150 μm DEBs.

To assess the safety and toxicity profile of the small-diameter 70–150 μm DEBs, we performed a retrospective review of patients who underwent transarterial chemoembolization with 70–150 μm DEBs to determine the incidence and severity of AEs in the form of clinically symptomatic AEs or LBI in patients with primary or secondary hepatic malignancies.

MATERIALS AND METHODS

Patients

This retrospective study was compliant with the Health Insurance Portability and Accountability Act and approved by the institutional review board with a waiver of informed consent. Based on the presumed size advantage of the 70–150 μm DEBs and on the limited available knowledge of their safety profile, we reserved their use for patients presenting with one of the following tumor characteristics: hypovascular tumors on cross-sectional imaging, tumors measuring ≤ 3 cm, and tumors with residual viable areas following other types of locoregional therapies. All other patients were treated with 100–300 μm DEBs. The retrospective review comprised 249 DEB transarterial chemoembolization procedures performed between July 2012 and December 2013. There were 56 70–150 μm DEB transarterial chemoembolization procedures performed in 46 patients. Of the 46 patients, 9 patients received other forms of locoregional therapies at the 70–150 μm DEB transarterial chemoembolization session and were excluded from the analysis; this left 37 patients for the present study. Table 1 summarizes baseline demographics, tumor characteristics, and laboratory values for the patient group.

70–150 μm DEB Transarterial Chemoembolization Procedure

The LC/DC Bead[M1] vial was loaded with 50 mg or 75 mg of doxorubicin (hepatocellular carcinoma [HCC], melanoma, squamous cell carcinoma, and leiomyosarcoma) or 100 mg of irinotecan (colorectal cancer). The 2-mL loaded solution was mixed with 12 mL of nonionic contrast material and 6 mL of 0.9% saline and injected into the segmental or subsegmental hepatic arteries using a 2.4-F or a 2.8-F microcatheter. Tumor devascularization and near stasis of the feeding vessels were considered

Table 1. Baseline Demographics, Tumor Burden, and Laboratory Values

Patient Characteristics	Mean Value (Range or Percentage)
Age (y)	66 (38–85)
Sex	
Female	4 (11%)
Male	33 (88%)
ECOG status	
0	23 (62%)
1	10 (27%)
2	4 (11%)
Tumor burden	
$< 25\%$	31 (83.8%)
25%–50%	5 (13.5%)
50%–75%	1 (2.7%)
Laboratory values prior to 70–150 μm DEB transarterial chemoembolization (per session)	
Hemoglobin (g/dL)	12.9 (9.7–15.6)
WBC ($\times 10^9$/L)	6.3 (1.1–11)
Platelets ($\times 10^9$/L)	187 (72–860)
ALP (U/L)	127 (47–404)
ALT (U/L)	80.1 (22–211)
AST (U/L)	66.2 (14–144)
Total bilirubin (mg/dL)	0.8 (0.3–2.6)

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DEB = drug-eluting bead, ECOG = Eastern Cooperative Oncology Group, WBC = white blood cell.