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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 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 (≤ 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.

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None of the authors have identified a conflict of interest.

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 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 trans-arterial 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 the endpoint for DEB delivery. Technical and clinical details of the 70–150 μm DEB transarterial chemoembolization sessions are depicted in **Table 2.**

AE Assessment

Clinically Symptomatic AEs—Baseline clinical and laboratory evaluations were performed before each 70–150 μm DEB transarterial chemoembolization session. Follow-up evaluations after 70–150 μm DEB trans-arterial chemoembolization were performed during the hospital stay and by telephone consultation 7 days after each 70–150 μm DEB transarterial chemoembolization session. AEs regarded as postembolization syndrome (PES) were abdominal pain, fever, nausea, vomiting, and fatigue. All AEs recorded were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (15). PES overall severity grade was regarded as the highest grade recorded among the five symptoms according to the Common Terminology Criteria for Adverse Events.

Liver/Biliary Injuries—Liver cross-sectional imaging was obtained using multidetector computed tomography or magnetic resonance imaging with a quadriphasic study protocol. Baseline imaging was performed within 1 month before each 70–150 μm DEB transarterial chemoembolization session. The mean overall imaging follow-up period after 70–150 μm DEB transarterial chemoembolization session per patient was 171 days (range, 21–391 d). LBI were considered to be due to the treatment if they were a new or aggravated finding after the 70–150 μm DEB transarterial chemoembolization session. LBI were categorized into four classes according to the definitions of the existing literature as follows: bile duct dilatation, portal vein narrowing, portal vein thrombosis, and biloma/liver infarct (13,16,17). LBI were also graded as (i) localized, when involving a liver sector, segment, or subsegment, or (ii) extensive, when extending into the main trunk or a lobar branch. All LBI were graded using the Common Terminology Criteria for Adverse Events.

Statistical Analysis

Statistical analysis comparing patient characteristics with and without LBI was performed to identify predictors of LBI after 70–150 μm DEB transarterial chemoembolization. Variables included patient age, gender, tumor type (HCC vs non-HCC), number of lesions treated, lesion size before and after 70–150 μm DEB transarterial chemoembolization, number of 70–150 μm DEB transarterial chemoembolization sessions (single vs multiple), use of other local radiation therapy before or after 70–150 μm DEB transarterial chemoembolization, effective 70–150 μm DEB transarterial chemoembolization dose delivered, Eastern Cooperative Oncology Group performance status score, and laboratory blood test values before and after 70–150 μm DEB transarterial chemoembolization. The percent differences in laboratory blood test values obtained before and after 70–150 μm DEB transarterial chemoembolization were calculated using the following formula: 100 × (laboratory value after 70–150 μm DEB transarterial chemoembolization – laboratory value before 70–150 μm DEB transarterial chemoembolization)/laboratory value before 70–150 μm DEB transarterial chemoembolization. A univariate logistic regression model was used to correlate patient characteristics and clinical factors with the development of LBI. Fisher exact test was used when zero count cells existed. All tests were two-sided, and P values ≤ .05 were considered statistically significant.

RESULTS

Clinically Symptomatic AEs

Clinically symptomatic AEs occurred in 67.4% (29 of 43) of the sessions. Grade 1 or 2 PES occurred in 65.1% (28 of 43) sessions. One patient who presented with grade 1 PES also had a self-limited grade 2 dysarthria immediately after 70–150 μm DEB transarterial chemoembolization that raised the concern of ischemic stroke. This dysarthria was later attributed to the intravenous sedation, and the patient was discharged in baseline condition. No grade 4 or 5 AEs were recorded. **Table 3** summarizes the incidence of clinically symptomatic AEs.

Liver/Biliary Injuries

LBI occurred in 11 (29.7%) patients (32% of HCC patients and 25% of non-HCC patients). All patients with LBI were asymptomatic and did not require any treatment during the mean clinical follow-up period from the time of appearance of LBI to the last clinical consultation of 373 days (range, 131–643 d). LBI were graded as 1 in eight patients and 2 in three patients. LBI were localized and occurred following one unique 70–150 μm DEB transarterial chemoembolization session. The most common LBI encountered were biloma/liver infarct (eight patients), biliary dilatation (four patients), portal vein thrombosis (three patients), and portal vein narrowing (two patients). The mean time between 70–150 μm DEB transarterial chemoembolization session and the appearance of LBI was 71 days (range, 21–223 d). LBI were detected on the first follow-up imaging study in nine patients (81.8%) and on the second follow-up imaging study in two patients (18.2%). The analysis comparing the characteristics of patients who had LBI with the characteristics of patients who did not have LBI did not reveal any statistically significant correlation between the presence of LBI and

the factors evaluated. Findings of the univariate analysis by patient and 70–150 μm DEB transarterial chemoembolization sessions are summarized in **Table 4.**

DISCUSSION

The present study shows that segmental/subsegmental 70–150 μm DEB transarterial chemoembolization had an acceptably low toxicity profile with most AEs being grade 1–2 and all LBI being clinically insignificant during a mean clinical follow-up period of < 1 year. Our initial experience with this new size of DEBs involved use in a selected population with distinct tumor characteristics (small diameter, hypovascular on cross-sectional imaging, or with small areas of residual disease). The justification for the use of 70–150 μm DEB trans-arterial chemoembolization in this patient population is based on the speculation that 70–150 μm DEBs would permit better particle penetration in the tumor in view of less well-developed feeding arteries usually associated with those tumor characteristics (18,19). The favorable results of the present study should be contemplated in light of the inherent differences among our patient population and the existing literature with the use of larger diameter DEBs.

PES is a self-limited condition and is considered the primary indication for inpatient care after transarterial chemoembolization (20). Although a precise and unbiased comparison of the present study findings with the existing literature is not feasible because of the differences among the patient population, the overall incidence of 67.4% of PES found in this study is within the range of the existing literature using larger DEBs. Malagari et al (21) found a PES incidence of 60.75%–86.5% across all sessions in 237 patients with HCC who underwent transarterial chemoembolization with 100–300 μm and 300–500 μm DEBs. In contrast, Padia et al (5) found an incidence of 40% and 8.3% of PES in patients treated with 300–500 μm and 100–300 μm particles, respectively. Nevertheless, fatigue was recorded as a distinct entity in their study with an incidence of 70% and 36.1%, respectively. Results of the PRECISION V (Prospective Randomised Study of Doxorubicin in the Treatment of Hepatocellular Carcinoma by Drug-Eluting Bead Embolisation) trial showed PES in 25% of patients treated with 300–500 μm and 100–300 μm particles (1). As pointed out by the authors, PES may not have been reported as such, possibly contributing to the low incidence observed. Regarding the severity grade of the AEs encountered, the incidence of 2.3% of grade 3 or higher AEs in the present study is lower than the suggested standards (22) and previously reported data, which ranges from 2.9% to 6.6% (23,24). The only patient with grade 3 abdominal pain reported in our series underwent partial splenic embolization at the time of 70–150 μm DEB transarterial chemoembolization, which possibly contributed to the aggravation of the symptoms.

The overall incidence of LBI of 29.7% found in our study is in the lower range of the existing literature. In a prospective phase II study of 100–300 μm DEB transarterial chemoembolization in 13 patients with hepatic neuroendocrine metastases, Bhagat et al (14) found an incidence of 54% of bilomas, with four patients requiring percutaneous drainage to address this complication. Guiu et al (13) demonstrated an incidence of LBI of 35.7% and 30.4% of sessions in patients with neuroendocrine cancer and HCC, respectively, following 100–700 μm DEB transarterial chemoembolization. In a recent study by Joskin et al (6), 83

patients with neuroendocrine cancer and with a high frequency of imaging abnormalities suggestive of LBI before treatment were treated with 165 sessions of 100–300 μm, 300–500 μm, or 500–700 μm DEB transarterial chemoembolization with an incidence of 44% of liver necrosis. This study also demonstrated a lower incidence rate of liver necrosis with 100–300 μm DEBs compared with < 300 μm DEBs (P = .010). As pointed out by the authors, this might be explained by a tendency of nontarget embolization of the healthy liver tissue in view of the inability of most DEBs > 300 μm to travel deep into the tumor vasculature because the mean size of tumor vessels is approximately 200 μm.

In the largest series published on the occurrence of biloma after conventional transarterial chemoembolization, Sakamoto et al (16) demonstrated that HCCs < 5 cm were a significant prognostic factor for the development of biloma. The potential lower incidence of biloma in patients with larger tumors is based on the possible protective factor produced by the dilated intratumoral blood space of larger HCCs that shift the chemoembolic agent away from the nontumoral liver parenchyma, resulting in a lower accumulation of the chemoembolic agent with a smaller chance of biliary damage. The nonsignificant difference (P = .66) in the incidence of LBI between patients with HCC and patients with non-HCC tumors in the present study (32% vs 25%) could be partially explained by the mean overall HCC diameter of only 3.4 cm and by the fact that only 8% of the patients with HCC had a tumor burden > 25% of the estimated total liver volume. In contrast, in patients with non-HCC tumors, the mean overall tumor size was 3.7 cm, and 33% of these patients had a tumor burden > 25% of the estimated total liver volume. The incidence of cirrhosis in patients with HCC in the present study was 68%, which is lower than expected compared with previous reports, in which 80% of patients with HCC were found to have cirrhosis on autopsy (25). The absence of the hypertrophied peribiliary plexus commonly observed in patients with cirrhosis could be one additional potential explanation for the nonsignificant incidence rate of LBI encountered. Finally, the higher frequency of drug delivery using a subsegmental level in roughly half of the 70–150 μm DEB transarterial chemoembolization sessions could facilitate the saturation of the adjacent peribiliary plexus, overcoming its known protective factor in cirrhotic patients (26).

The present study has several limitations. First, the indication for the use of 70–150 μm DEB transarterial chemoembolization was limited to a selected patient population with certain tumor characteristics. As a result, comparisons with other patient groups described in the literature on DEB transarterial chemoembolization are not directly applicable. Nevertheless, this study provides early evidence that AEs associated with 70–150 μm DEB transarterial chemoembolization are equivalent to AEs that have been reported across different patient populations. Second, the inherent limitations of a retrospective investigation resulted in a lack of consistency in acquisition of laboratory studies, potentially limiting use of laboratory values as an indication of the development of LBI, as previously reported by some authors (13). Third, efficacy (response rate) was not recorded; this was an intentional omission because the present study was not designed to assess response in view of the obvious selection bias of the patient study population and the intrinsic limitations in finding a control group. Finally, the assessment of the degree of stasis of the selected vessels could potentially provide some relevant association with the incidence of LBI, as previously reported (4).

Because of the lack of consensus on how to assess the degree of stasis of a treated vessel and the retrospective nature of our study, this variable was not incorporated in the analysis.

In conclusion, segmental/subsegmental 70–150 μm DEB transarterial chemoembolization was considered safe in patients with small-diameter lesions, hypovascular lesions, and lesions with small areas of residual disease. These early data on the use of 70–150 μm DEBs suggest that AEs after 70–150 μm DEB trans-arterial chemoembolization in this selected patient population are similar to AEs reported after DEB transarterial chemoembolization using larger particles. Finally, no predictors for the development of LBI were identified. On the basis of these results, we use this new class of DEBs with fewer restrictions in our daily clinical practice. Further investigations using this new chemoembolic platform in an expanded study population are recommended to confirm the present findings.

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ABBREVIATIONS

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

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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.

Table 2

Technical Characteristics of 70–150 μm DEB Transarterial Chemoembolization Sessions

	HCC	Colorectal Cancer	Melanoma	Squamous Cell Carcinoma	LMS	Total
No. patients	25	5	5	1	1	37
Mean no. 70–150 μm DEB transarterial chemoembolization sessions per patient	1.1 (1–2)	1 (1)	1.8 (1–3)	1	1	1.16
Lesion diameter (cm)	3.2 (3–6.6)	3.2 (1.1–3.7)	4.6 (0.7–6.8)	4.2	1.4	3.4
Total no. 70–150 μm DEB transarterial chemoembolization sessions	27	5	9	1	1	43
Other LRT at target lesion	100–300 μm DEB transarterial chemoembolization (n = 4); percutaneous ablation (n = 3)	No	Percutaneous ablation (n = 1)	Percutaneous ablation + 100–300 μm DEB transarterial chemoembolization (n = 1)	No	9
Treatment location per session						
Segmental	14	3	5	1	1	24
Subsegmental	13	2	4	NA	NA	19
Mean 70–150 μm DEB transarterial chemoembolization dose per target lesion	31 (10–50)*	41 (25–100)†	56 (35–90)*	60*	20*	NA
Hospital admissions (mean no. d)	0.6 (0–2)	1.2 (1–2)	1.2 (1–2)	1	1	0.8

DEB = drug-eluting bead, HCC = hepatocellular carcinoma, LMS = leiomyosarcoma, LRT = local radiation therapy, NA = not available.

*Doxorubicin.

†Irinotecan.

Table 3

Incidence of Clinically Symptomatic AEs (per Session)

AEs	No. (%)
Grade 1–2	
Fatigue	21 (48.8%)
Abdominal pain	20 (46.5%)
Fever	11 (25.6%)
Nausea	10 (23.2%)
Vomiting	5 (11.6%)
Groin hematoma	4 (9.3%)
Dysarthria	1 (2.3%)
Grade 3	
Abdominal pain*	1 (2.3%)

AEs = adverse events.

* Patient underwent partial splenic embolization at the same session.

Table 4

Summary of Univariate Logistic Regression Model Predicting the Probability of Having Liver Complications

Factor	OR	95% CI of OR		*P* Value
Gender (female vs male)	0.767	0.036	6.862	.824
Age (every 1-y increase)	0.990	0.913	1.066	.793
Type of tumor (HCC vs non-HCC)	1.412	0.315	7.661	.660
No. 70–150 μm DEB transarterial chemoembolization sessions (single vs multiple sessions)	1.029	0.248	4.393	.969
Other LRT before or after 70–150 μm DEB transarterial chemoembolization (yes vs no)	1.905	0.391	8.887	.413
Systemic therapy (yes vs no)	1.018	0.184	4.773	.983
Level of treatment (segmental vs subsegmental)	1.029	0.248	4.393	.969
ECOG class (0 vs 1 + 2)	1.574	0.364	6.734	.537
Overall lesion size before transarterial chemoembolization (cm; every 1-cm increase)	1.091	0.752	1.665	.656
Effective dose (per lesion; every 1-mg increase)	0.988	0.957	1.018	.412

Note–Absolute laboratory values and variations in percentage before and after DEB transarterial chemoembolization with LC/DC Bead[M1] were omitted because of the nonsignificant values encountered.

CI = confidence interval, DEB = drug-eluting bead, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, LRT = local radiation therapy, OR = odds ratio.