Radiology

Superselective Chemoembolization of HCC: Comparison of Short-term Safety and Efficacy between Drug-eluting LC Beads, QuadraSpheres, and Conventional Ethiodized Oil Emulsion[1]

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Purpose: To study the comparative short-term safety and efficacy of transcatheter arterial chemoembolization (TACE) with drug-eluting LC Beads loaded with doxorubicin (DEBDOX), doxorubicin-eluting QuadraSpheres (hqTACE), and conventional TACE using ethiodized oil for superselective C-arm computed tomography (CT)-guided treatment of hepatocellular carcinoma (HCC) after the onset of drug shortages.

Materials and Methods: From March 2010 to March 2011, 166 patients with HCC were treated with 232 superselective TACE procedures using C-arm cone-beam CT at one institution. Patients underwent treatment depending on the availability of materials after the onset of drug shortages. Conventional TACE with doxorubicin, cisplatin, and Ethiodol was performed for 159 procedures, DEBDOX TACE was performed for 47, and hqTACE was performed for 26. Toxicity and objective response were compared at 3 months after treatment. Data were stratified for the high-risk population (Child-Pugh class B, performance status 1, bilobar disease, and/or postresection recurrence) and initial versus repeat treatment. Kruskal-Wallis H test, Mann-Whitney *U* test, and Fisher exact test were used to compare the groups, with Bonferroni correction where needed.

Results: Whole liver response rates trended higher for conventional TACE (conventional TACE, 65.4%; DEBDOX, 63.8%; hqTACE, 53.8%) (P = .085). Only minor trends for differences in toxicity were observed between the three groups. Low-risk patients had higher whole liver (P = .001) and treated lesion (P = .007) response rates when treated with conventional TACE, but no significant differences were seen for DEBDOX and hqTACE. Treatment-naive patients also had higher whole liver (P = .012) and treated lesion (P = .056) response rates. No advantages for drug-eluting microspheres were found.

Conclusion: Within statistical power limitations, overall toxicity and efficacy were equivalent in patients treated with LC Beads, QuadraSpheres, or ethiodized oil emulsions, including in high-risk patients, when performed superselectively with cone-beam C-arm CT guidance.

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Transcatheter arterial chemoembolization (TACE) is the most commonly used local-regional treatment for unresectable hepatocellular carcinoma (HCC) (1). The convention for decades has been to deliver concentrated chemotherapeutic solutions in an ethiodized oil emulsion (Ethiodol; Savage Laboratories, Melville, NY), with or without particulate embolization, which results in a favorable pharmacokinetic profile (2). However, this technique may result in inconsistent drug delivery and retention (3). Alternative vehicles have been developed by using calibrated ion-exchange polymer microspheres to allow consistent embolization and a predictable retention and elution of agents such as doxorubicin. Commercially available drug-eluting microsphere products include LC Beads (Biocompatibles/BTG, Farnham, United Kingdom) and QuadraSpheres (BioSphere/Merit Medical, South Jordan, Utah). These new vehicles may offer the opportunity to implement a higher level of standardization to HCC treatment (1).

Previous studies have shown that TACE with drug-eluting microspheres has an improved pharmacokinetic profile and results in effective tumor killing in both preclinical animal models and clinical studies in humans (4–8). The PRECISION V randomized trial did not reach its primary end point of improved objective response at 6 months, but did identify relative benefit of using drug-eluting microspheres to achieve a higher response rate in high-risk patients and lower toxicity overall (8). Mean total sum of diameters was almost 9 cm and the mean dose of doxorubicin was 142 mg, indicating a patient population with advanced disease that was probably not amenable to superselective (subsegmental) treatment. The use of cone-beam C-arm computed tomography (CT) (9) was not mandated and not described. Newer data now show that the use of C-arm CT results in improved arterial mapping, lesion detection, completeness of treatment, and possibly overall survival (10), suggesting that routine use of C-arm CT should be considered optimal or even standard of care.

The Ethiodol, cisplatin, and doxorubicin shortages in the United States during the past 4 years have necessitated improvisation and revision of protocols for TACE. The purpose of this study was to compare the short-term safety and efficacy of TACE with drug-eluting LC Beads loaded with doxorubicin (DEBDOX), TACE with doxorubicin-eluting QuadraSpheres (hqTACE), and conventional TACE using ethiodized oil for superselective, C-arm CT-guided treatment of HCC after the onset of drug shortages.

Advances in Knowledge

- Objective response rates (54%–65%) and disease control rates (69%–85%) after single treatments using drug-eluting microspheres or ethiodized oil emulsion were equivalent when used superselectively with C-arm CT guidance to treat hepatocellular carcinoma.
- Hepatic and systemic toxicity were also equivalent between preparations.
- High-risk patients (Child-Pugh class B, performance status 1, bilobar disease, and/or recurrence after resection or ablation) had poorer outcomes than did low-risk patients when treated with ethiodized oil emulsion (objective response $P = .001$, disease control $P = .007$) or LC Beads (disease control $P = .04$), but overall, for treatment of high-risk patients, no advantages were found for drug-eluting microspheres.
- Treatment-naive patients had higher objective response rate ($P = .012$) and disease control rate ($P = .003$) than did previously treated patients.

Implications for Patient Care

- Favorable patient outcomes after chemoembolization of hepatocellular carcinoma were achieved despite drug shortages.
- Meticulous superselective catheterization and use of cone-beam C-arm CT resulted in equivalent results using drug-eluting microspheres or ethiodized oil emulsion.

Materials and Methods

Study Design

Data were handled in accordance with the Health Insurance Portability and Accountability Act. The institutional review board approved this retrospective study. In the 12 months following the onset of shortages of Ethiodol and lyophilized cisplatin and doxorubicin (March 2010 to March 2011), 166 patients with HCC were treated by using 232 superselective TACE procedures at a single institution. Patients had no evidence of extrahepatic metastasis and did not undergo concomitant systemic treatment with sorafenib (Onyx Pharmaceuticals, South San Francisco, Calif). During this same time period, 17 patients with earlier stage disease were treated with radiofrequency ablation, and 27 patients with later stage disease (eg, portal vein tumor thrombus, infiltrative disease, progression after

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Abbreviations:
DEBDOX = drug-eluting LC Bead loaded with doxorubicin
HCC = hepatocellular carcinoma
hqTACE = doxorubicin-eluting QuadraSphere TACE
TACE = transcatheter arterial chemoembolization

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Guarantors of integrity of entire study, F.D., D.Y.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, F.D., E.Q.W., M.G.E.H.L., M.H.K.A., W.T.K., D.Y.S.; clinical studies, F.D., M.H.K.A., J.D.L., G.L.H., W.T.K., L.V.H., D.Y.S.; experimental studies, F.D., W.T.K.; statistical analysis, F.D., E.Q.W., M.G.E.H.L.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

previous TACE, or a tumor burden too large to treat by one TACE session) were treated with yttrium 90 radioembolization. The treatment modality was chosen by consensus-derived algorithm at a multidisciplinary hepatobiliary tumor board or at a multidisciplinary liver transplant board.

Baseline patient characteristics are summarized in Table 1. A total of 121 patients underwent 159 conventional TACE procedures with concentrated chemotherapeutic and Ethiodol (doxorubicin + cisplatin [n = 122] or doxorubicin alone after lyophilized cisplatin supplies were exhausted [n = 37]), 45 patients underwent 47 DEBDOX procedures, and 26 patients underwent 26 hqTACE procedures. The selection of drug preparation was conventional TACE as the default, with DEBDOX or hqTACE implemented after the distribution of Ethiodol was discontinued and stockpiled supplies were depleted. Individual treating physicians alternated between DEBDOX and hqTACE depending on availability of materials. TACE procedures were performed by six different physicians (J.D.L., G.L.H., N.K., W.T.K., L.V.H., D.Y.S.), with 2–14 years of posttraining experience in hepatic arterial interventions. Retrospective data collection was performed by four authors (F.D., E.Q.W., M.G.E.H.L., M.H.K.A.) who did not perform clinical TACE procedures.

All TACE procedures were performed by using digital subtraction angiography and cone-beam C-arm CT guidance, as previously reported (9). Maximum catheter selectivity was achieved by using a microwire (0.014-inch Transend or Fathom; Boston Scientific, Natick, Mass) and a microcatheter (2.4-F Progreat, Terumo Medical, Somerset, NJ; or 2.3-F Prowler Plus or 1.9-F Prowler Select LP ES, Codman/J&J, Raynham, Mass), with administration from subsegmental, segmental, or lobar branches afferent to the tumors, often with the microcatheter wedged (Fig 1). Maximum drug dosages per procedure were 20 mL Ethiodol, 50 mg doxorubicin, 50 mg cisplatin, each suspended in 10 mL iohexol (Omnipaque 300; GE Healthcare, Waukesha, Wisc), with gelatin sponge slurry (Surgifoam, Ethicon, Somerville, NJ) added in cases of arterioportal or arteriovenous shunt placement in the conventional TACE group; 150 mg doxorubicin (75 mg in each of two vials, 100–300 μm and 300–500 μm LC Beads) in the DEBDOX group (8); and 100 mg doxorubicin (50 mg in each of two vials, 50–100 μm QuadraSpheres) in the hqTACE group (11). After lyophilized cisplatin supplies were depleted, conventional TACE was performed by using only doxorubicin, up to 100 mg maximum.

Preparations were administered until stasis in the conventional TACE group, until near-stasis in the DEBDOX group, and until second onset of stasis at least 5 minutes after initial stasis in the hqTACE group, as recommended by the manufacturers. Real-time subtraction fluoroscopy (roadmap) was utilized to minimize reflux into nontarget vessels. Superselective treatment of multiple feeding branches was performed until nonenhanced C-arm CT showed complete Ethiodol or iodinated contrast medium retention in the targeted tumors (9) and angiography showed no residual enhancement. Patients in the conventional TACE group with residual robust arterial flow received gelatin sponge slurry, and patients in DEBDOX and hqTACE groups with residual robust arterial flow received additional bland embolization with the same size bland embolic spheres until reaching the desired angiographic end point. All identified disease, whether unilobar or bilobar, was targeted for treatment.

Patients were clinically re-evaluated 7–14 days after TACE and comprehensively again at 3 months. The mean follow-up period after TACE was 85 days (range, 24–129 days), 91 days (range, 61–104 days), and 88 days (range, 56–113 days) for conventional TACE, DEBDOX TACE, and hqTACE, respectively. Collected data included clinical status, laboratory values (blood cell counts, liver enzymes [aspartate aminotransferase and alanine aminotransferase, alkaline phosphatase], total bilirubin, albumin, creatinine, alpha-fetoprotein) and imaging (contrast medium–enhanced multiphasic CT or MR imaging). If a patient received another treatment before the 3-month follow-up, the data gathered immediately before that treatment were used so that all data reflected results after one treatment. The objective tumor response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (12). Both treated lesion and whole liver responses were recorded. One blinded author (F.D., with 3 years of posttraining experience in hepatic arterial interventions and diagnostic radiology) performed overreads of all clinical image interpretations. All recorded treatment-related adverse events during the 3-month follow-up period were graded by using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (13).

To compare our results with those reported in the PRECISION V trial, we also performed subset analyses in patients defined as high risk in that trial: Child-Pugh class B, Eastern Cooperative Oncology Group performance status 1, bilobar disease, and/or postresection recurrence (8). We also performed subset analysis stratified to treatment-naive patients versus repeat TACE patients to address the issue of diminishing benefit.

Statistical Analysis

Statistical analyses were performed by one author (F.D.) with guidance from a statistician. A commercial statistical software package (SPSS for Windows, version 16.0; SPSS, Chicago, Ill) was used for data analysis. All continuous variables proved to have a nonnormal distribution (Kolmogorov-Smirnov test). The Kruskal-Wallis H test was used to test overall differences among the three treatment groups. The Mann-Whitney U test was used to test differences pairwise between two groups for continuous variables, and the Fisher exact test for categorical variables. Bonferroni correction was used for multiple comparisons. P values $< .05$ were considered to indicate statistically significant difference.

Table 1

Baseline Patient Characteristics

Characteristic	Conventional TACE	DEBDOX TACE	hqTACE	*P* Value*
M/F	121/38	39/8	20/6	.647
Age (y)†	66 (29–85)	64 (44–88)	67 (38–80)	.849
Etiology				.090
Hepatitis B virus	48	7	9	
Hepatitis C virus	68	34	12	
Alcohol and other	43	6	5	
BCLC stage				.571
A	45	9	8	
B	101	35	15	
C	13	3	3	
Child-Pugh status				.926
A	113	35	19	
B	41	10	6	
C	5	2	1	
MELD score	9 (6–21)	9 (6–24)	9 (6–21)	.491
ECOG performance status 0/1	149/10	46/1	23/3	.248
No. of high-risk patients‡	85 (53.5)	25 (53.2)	11 (42.3)	.581
Laboratory values				
White blood cell count (10^9/L)†	4.7 (1.3–13)	4.3 (1.1–10.4)	4.0 (1.7–7.0)	.788
Platelet count (10^9/L)†	101 (31–482)	95 (29–253)	100 (23–240)	.927
Hemoglobin (g/dL)†	13.0 (8.1–17.0)	13.2 (9.7–16.9)	13.3 (8.3–15.5)	.341
Serum aspartate aminotransferase (IU/L)†	52 (12–416)	67 (19–245)	54 (27–268)	.148
Serum alanine aminotransferase (IU/L)†	49 (14–332)	63 (18–230)§	57 (23–229)	.027
Serum total bilirubin (mg/dL)†	0.9 (0.2–4.7)	1.0 (0.4–3.6)	1.0 (0.4–3.3)	.837
Serum alkaline phosphatase (IU/L)†	134 (49–507)	134 (48–393)	152 (32–862)	.275
Serum albumin (g/dL)†	3.5 (1.7–4.7)	3.4 (1.9–4.6)	3.4 (2.0–4.3)	.740
International normalized ratio†	1.2 (0.7–1.8)	1.1 (1.0–3.8)	1.2 (1.0–1.8)	.488
Serum creatinine (mg/dL)†	0.9 (0.4–3.3)	1.0 (0.6–1.7)	0.9 (0.4–1.6)	.982
Serum α-fetoprotein (ng/mL)†	35 (2–70 976)	36 (2–3993)	51 (2–113 543)	.330
Serum α-fetoprotein in patients with baseline $>$ 10 ng/mL (ng/mL)	85 (96 patients)	106 (34 patients)	155 (21 patients)	.085
Tumor burden and distribution				
Unifocal/multifocal	64/95	17/30	12/14	.712
Unilobar/bilobar	101/58	28/19	19/7	.531
No. of lesions‖	2 (4.2) [1–50]	2 (6.0) [1–50]	2 (2.8) [1–8]	.590
Largest lesion diameter (cm)‖	3.1 (4.2) [0.7–23.0]	2.5 (3.8) [0.9–16.0]	4.1 (5.2) [1.3–13.9]	.131
Total sum of lesion diameters (cm)‖	5.9 (7.6) [1.1–50]	5.4 (7.4) [1.5–50]	7.8 (8.1) [1.3–16.5]	.509
First treatment/repeat treatment**	74/85 (1–7)	21/26 (1–6)	7/19 (1–8)	.182
Chemotherapeutic dose delivered (mg)**	55 (4.0–110)	75 (3.8–150)#	50 (8–100)#	.014
Ethiodol volume administered (mL)**	10.0 (1.5–20)	0	0	
Median no. of particle embolic administered	0	2.0 g hydrated (~200 000 microspheres)	25 mg dry (~140 000 microspheres)	
Procedure time (min)**	100 (36–209)	96 (24–240)	104 (60–159)	.635

Note.—Unless otherwise indicated, data are number of patients, with ranges in parentheses. BCLC = Barcelona Clinic Liver Cancer, ECOG = Eastern Cooperative Oncology Group, MELD = model for end-stage liver disease.

* Overall *P* values from Kruskal-Wallis H test.

† Data are medians, with ranges in parentheses.

‡ High risk defined as ECOG PS = 1 or Child-Pugh status B or C or postcurative recurrence. Data in parentheses are percentages.

§ Alanine aminotransferase in the DEBDOX group was higher than that in the conventional TACE group (Bonferroni-corrected Mann-Whitney *U* test, $P = .036$).

‖ Data are medians, with means in parentheses and ranges in brackets.

The chemotherapeutic dose delivered in the DEBDOX group was higher than that in the hqTACE group (Bonferroni-corrected $P = .085$) and the conventional TACE group (Bonferroni-corrected $P = .018$). Conventional TACE values include doxorubicin dose in patients who received only doxorubicin and sum of doxorubicin and cisplatinum doses in patients who received combination therapy.

** Data in parentheses are the range.

Figure 1

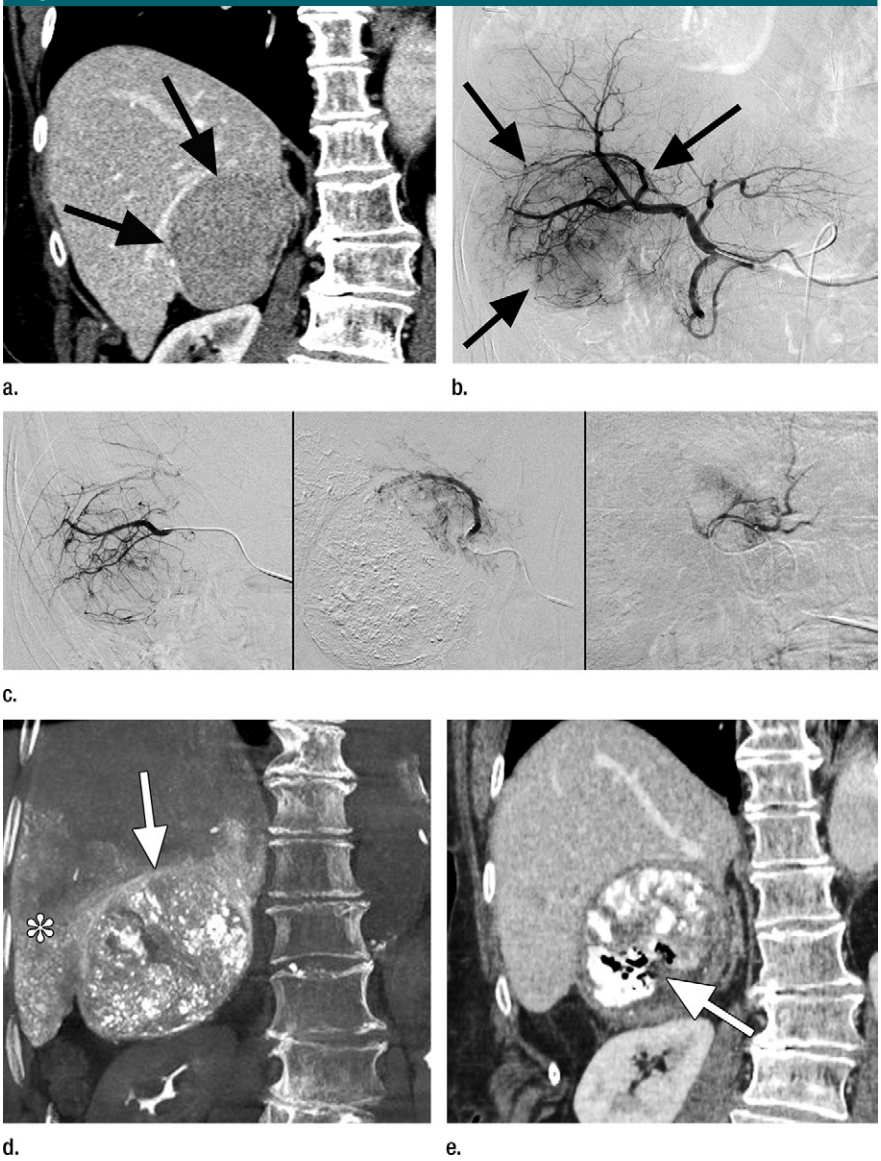

Figure 1: Images in a 79-year-old woman with nonalcoholic steatohepatitis and cirrhosis who presented with right upper quadrant pain and was found to have an 8-cm mass centered in segment 6, confirmed to be HCC at biopsy. **(a)** Coronal reconstruction of a venous phase contrast-enhanced CT shows an exophytic mass with early washout (arrows). **(b)** Digitally subtracted angiogram obtained 5 months later shows interval growth and multisegmental arterial supply to the tumor (arrows), which could have been treated conveniently with right lobar TACE. **(c)** Instead, individual segmental and subsegmental branches of segments 6, 5, and 1 were superselectively catheterized with a 2.4-F microcatheter and treated with an emulsion of Ethiodol (20 mL), doxorubicin (50 mg), and cisplatin (50 mg). Because of arterioportal shunt placement, a small amount of gelatin sponge slurry was added to the emulsion. **(d)** Coronal reconstruction of an unenhanced C-arm CT performed after TACE confirmed complete uptake in the lesion and its pseudocapsule (arrow), with minimal nontarget deposition in adjacent hepatic parenchyma (*). Patient had grade 1 nausea only and was discharged 20 hours later. **(e)** Follow-up CT image 3 months later shows modified Response Evaluation Criteria in Solid Tumors complete response, with massive necrosis associated with sterile gas formation (arrow). Child-Pugh class and model for end-stage liver disease scores were unchanged. She has undergone six additional superselective treatments for recurrent and metachronous disease over 47 months and remains Child-Pugh class A and Eastern Cooperative Oncology Group performance status 0.

Results

Patient characteristics are listed in Table 1. The baseline variables in the three groups were comparable. One-hundred two treatments were in treatment-naive patients, and 130 were re-treatments of patients with residual or recurrent disease. Fifty-five patients underwent multiple treatments, 26 of whom received two different preparations. Data are listed per procedure; hence, patients who underwent two procedures using two different preparations were included in two different groups independently. Only baseline alanine aminotransferase in the DEBDOX group (median, 67 IU/L) was higher than that in the conventional TACE group (median, 49 IU/L; Bonferroni-corrected Mann-Whitney *U* test, $P = .036$), which is of doubtful clinical significance. The tumor burden, as measured by total sum of tumor diameters, was higher in the hqTACE group, but not significantly (median, 7.8 cm for hqTACE, 5.9 cm for conventional TACE, 5.4 cm for DEBDOX; $P = .509$). The doxorubicin dose delivered in the DEBDOX group (median, 75 mg) was higher than that in the hqTACE group (median, 50 mg; $P = .085$) and the conventional TACE group (median, 55 mg; $P = .018$). All procedures were technically successful, with no major procedural complications requiring additional hospitalization or intervention (14). All patients were observed overnight, and 229 (98.7%) were discharged within 24 hours after the procedure.

Clinical adverse events (129 events after 232 procedures) included fever, pain, nausea, fatigue, weight loss, and alopecia, but were mostly limited to grade 1 and 2 (Table 2). Grade 3 clinical toxicity was rare, reported for the conventional TACE group (one patient with grade 3 nausea and vomiting and one patient with grade 3 fatigue). One patient in the DEBDOX group developed a grade 3 hepatic abscess, but paradoxically in the contralateral untreated lobe. No patients had grade 4 or 5 toxicities. The number of patients who reported fever in the hqTACE group trended higher than that in the

Table 2

Clinical Toxicities according to Common Terminology Criteria for Adverse Events, Version 4.03

	Conventional TACE		DEBDOX TACE		hqTACE		
Toxicity and Grade	No. of Patients	95% CI	No. of Patients	95% CI	No. of Patients	95% CI	*P* Value*
Fever							.082
0	150 (94.3)	89.2, 97.2	44 (93.6)	82.8, 97.8	21 (80.8)	62.1, 91.5	
1	7 (4.4)	1.9, 9.2	3 (6.4)	1.7, 18.6	5 (19.2)	8.5, 37.9	
2	2 (1.3)	0.2, 4.9	…	…	…	…	
Pain							.388
0	140 (88.1)	82.1, 92.2	38 (80.9)	67.5, 89.6	22 (84.6)	66.5, 93.9	
1	17 (10.7)	6.8, 16.5	7 (14.9)	7.4, 27.7	3 (11.5)	3.0, 31.3	
2	2 (1.3)	0.2, 4.9	2 (4.3)	0.7, 15.7	1 (3.8)	0.2, 21.6	
Nausea and vomiting							.513
0	149 (93.7)	88.4, 96.8	43 (91.5)	80.1, 6.6	23 (88.5)	71.0, 96.0	
1	8 (5.0)	2.4, 10.0	3 (6.4)	1.7, 18.6	2 (7.7)	1.3, 26.6	
2	1 (0.6)	0.03, 4.0	1 (2.1)	0.1, 12.7	1 (3.8)	0.2, 21.6	
3	1 (0.6)	0.03, 4.0	…	…	…	…	
Fatigue							.229
0	130 (81.8)	75.0, 87.0	41 (87.2)	74.8, 94.0	17 (65.4)	46.2, 80.6	
1	21(13.2)	8.8, 19.4	4 (8.5)	2.8, 21.3	8 (30.8)	16.5, 50.0	
2	7 (4.4)	1.9, 9.2	2 (4.3)	0.7, 15.7	1 (3.8)	0.2, 21.6	
3	1 (0.6)	0.03, 4.0	…	…	…	…	
Weight loss							.142
0	152 (95.6)	90.8, 98.1	47 (100)	90.6, 100	23 (88.5)	71.0, 96.0	
1	6 (3.8)	1.5, 8.4	0	…	2 (7.7)	1.3, 26.6	
2	1 (0.6)	0.03, 4.0	0	…	1 (3.8)	0.2, 21.6	
Alopecia							.999
0	153 (96.2)	91.6, 98.5	46 (97.9)	87.3, 99.9	25 (96.2)	78.4, 99.8	
1	6 (3.8)	1.5, 8.4	1 (2.1)	0.1, 12.7	1 (3.8)	0.2, 21.6	
Abscess							.529
0	159 (100)	97.1, 100	46 (97.9)	87.3, 99.9	26 (100)	84.0, 100	
1	…	…	…	…	…	…	
2	…	…	…	…	…	…	
3	…	…	1 (2.1)	0.1, 12.7	…	…	

Note.—Data in parentheses are percentages. CI = confidence interval.

* *P* values represent Fisher exact test; overall *P* value results from 4 × 3 matrix, grade 0–3 x TACE vehicle.

conventional TACE group (Bonferroni-corrected Fisher exact test, $P = .082$). Changes in laboratory values within 3 months after TACE were mostly mild, expected, and transient (Table 3). The changes in serum creatinine (improvement) and alkaline phosphatase (elevation) after treatment trended higher in the DEBDOX group than in the conventional TACE group (Kruskal-Wallis, $P = .053$, 0.140). Elevation of Child-Pugh score was less pronounced in the conventional TACE group ($P = .446$), and elevation of model for end-stage liver disease score was less pronounced in the DEBDOX group ($P = .505$), but neither reached statistical significance. No differences were found within the conventional TACE group between patients who received doxorubicin versus those who received both doxorubicin and cisplatin.

Imaging-confirmed complete response, partial response, stable disease, and progressive disease were analyzed separately for the whole liver and for treated lesions (Fig 2). The whole liver response rates at 3 months were 62.9% (95% confidence interval [CI]: 55.2%, 70.0%), 59.6% (95% CI: 45.3%, 72.3%), and 38.5% (95% CI: 22.4%, 57.5%), respectively, for conventional TACE group, DEBDOX group, and hqTACE group. The rate in the conventional TACE group trended higher than that in the hqTACE group (Bonferroni-adjusted, $P = .085$). However, the treated lesion-specific response rates were 65.4% (95% CI: 57.7%, 72.3%), 63.8% (95% CI: 50.0%, 76.0%), and 53.8% (95% CI: 35.5%, 71.3%), respectively, for conventional TACE group, DEBDOX group, and hqTACE group, with no significant differences between the groups. The lower whole liver response for hqTACE was due to appearance of new lesions in more

Table 3

Change in Laboratory Values after Treatment

	Conventional TACE	DEBDOX TACE	hqTACE	*P* Value*
White blood cell count (%)	0.0 (−40.5 to +267.3)	6.1 (−43.5 to +91.2)	−5.0 (−40.7 to +44.4)	.812
Platelet count (%)	−2.8 (−62.1 to +261.4)	−3.9 (−61.3 to +65.8)	6.5 (−40.8 to +73.9)	.783
Hemoglobin (%)	−2.8 (−26.9 to +36.8)	−1.5 (−32.8 to +29)	−3.8 (−20.4 to +8.1)	.742
Aspartate aminotransferase (%)	0.0 (−69.6 to +1820.6)	−5.8 (−50 to +297.6)	−3.8 (−50 to +409.3)	.738
Alanine aminotransferase (%)	−6.6 (−76.7 to +653.1)	−9.0 (−60.3 to +140)	−11.1 (−51.0 to +273.4)	.484
Total bilirubin (%)	0.0 (−55.6 to +500)	0.0 (−58.3 to +80)	14.3 (−60 to +410)	.606
Alkaline phosphatase (%)	3.2 (−65.9 to +307.9)	11.4 (−35.7 to +193.3)	14.4 (−47.1 to +116.6)	.140
Albumin (%)	−4.8 (−37.1 to +41.2)	−4.7 (−38.7 to +26.3)	−5.9 (−40 to +15)	.503
International normalized ratio (%)	0.0 (−27.8 to +75)	0.0 (−68.4 to +35.3)	0.0 (−35.3 to +20)	.847
Creatinine (%)	0.0 (−36.8 to +71.4)	−7.7 (−62.3 to +44.9)	0.0 (−18.2 to +80)	.053
Change in MELD score†	0.6 (0.7) [−3.5 to +4.6]	0.5 (0.0) [−2.6 to +3.0]	0.8 (0.7) [−4.7 to +7.1]	.505
Change in Child-Pugh score†	0.34 (0.0) −2 to+3]	0.46 (0.0) [−2 to +3]	0.53 (1.0) [−3 to +4]	.446

Note.—Unless otherwise indicated, data are medians, with ranges in parentheses. MELD = model for end-stage liver disease.

* *P* values shown are overall results of Kruskal-Wallis H test.

† Data are means, with medians in parentheses and ranges in brackets.

Figure 2

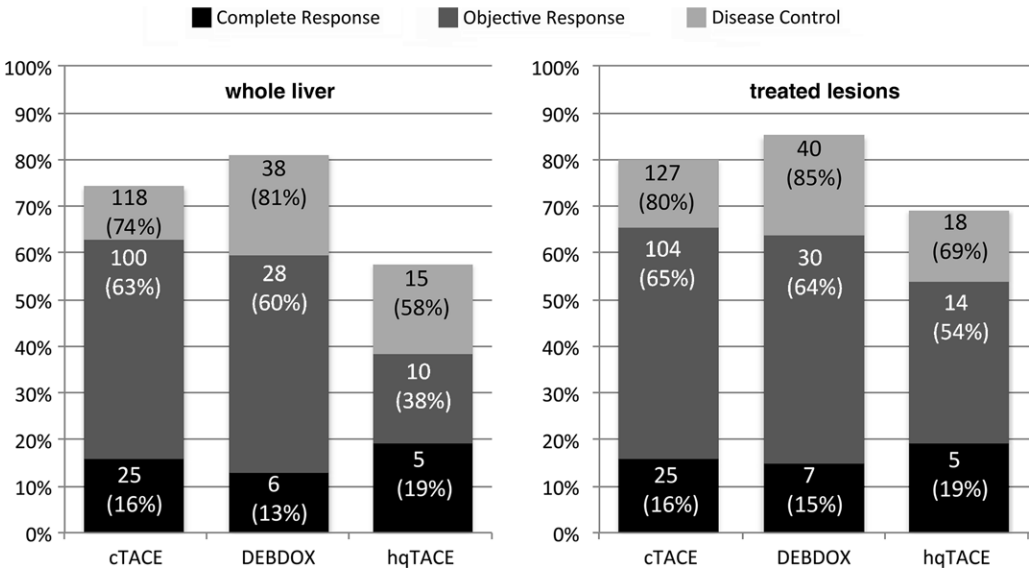

Figure 2: Graphs show response to treatment according to TACE preparation, as measured by modified Response Evaluation Criteria in Solid Tumors and stratified according to whole liver and treated lesions. No significant differences were found between the groups, except the whole liver objective response in the conventional TACE *(cTACE)* group trended higher than that in the hqTACE group ($P = .029$; Bonferroni-corrected Mann Whitney *U* test, $P = .085$).

patients ($n = 10$), not due to progressive disease in treated lesions. The number of subjects who underwent hqTACE was small, and their total tumor burden trended higher than in the other groups, which may partially explain this observation. No difference within the conventional TACE group was found between patients who received one drug versus both (uncorrected Mann Whitney, $P = .580$).

Subset analysis on the 121 (52%) high-risk patients as defined in PRECISION V trial revealed similar toxicity results compared with those in the cohort's lower risk patients. No differences in clinical toxicity or laboratory toxicities were seen between the treatment groups, including doxorubicin-related toxicity. Objective response and disease control rates were higher in low-risk patients than in high-risk patients for conventional TACE and DEBDOX, but there were no significant

Figure 3

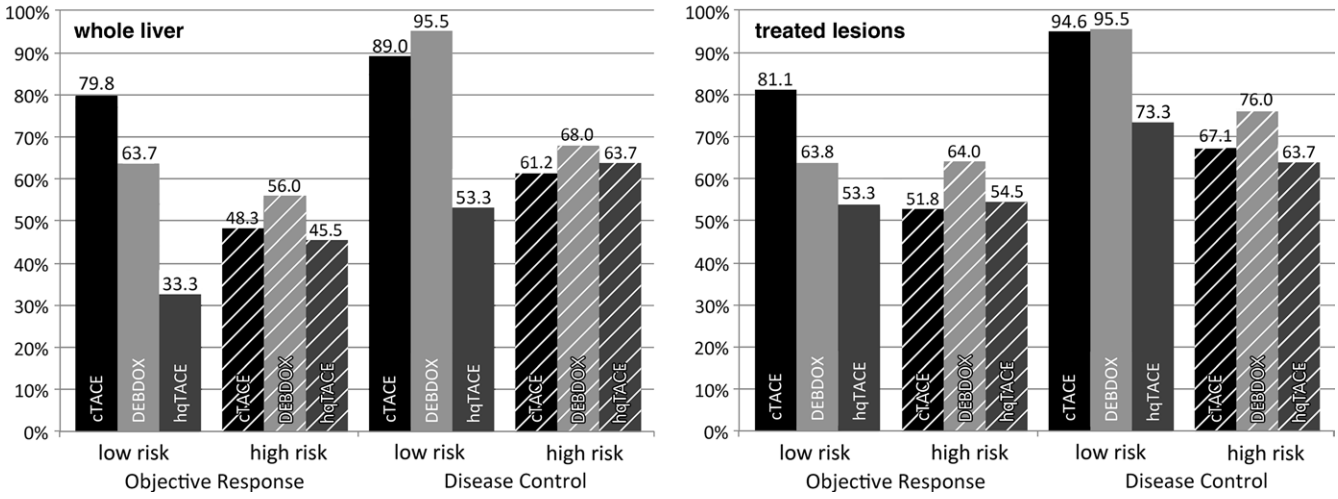

Figure 3: Graphs show response to treatment in low-risk (solid bars) and high-risk subpopulations (hashed bars), consisting of patients who were Child-Pugh class B, had Eastern Cooperative Oncology Group performance status 1, had bilobar disease, and/or had recurrence after prior resection or ablation. For conventional TACE *(cTACE)*, the objective response rate in low-risk patients was higher than that in high-risk patients for both whole liver (Mann-Whitney *U* test $P = .001$) and treated lesions ($P = .007$). Likewise, the disease control rate was also higher in whole liver ($P = .001$) and treated lesions ($P = .001$). For DEBDOX, no significant differences were found in objective response rates, but the disease control rate was higher in low-risk patients than in high-risk patients for whole liver ($P = .040$) and a trend was found in treated lesions ($P = .076$). No differences were found for hqTACE. Overall, in the treatment of high-risk patients, no significant advantages were found for any of the preparations ($P = .760$ for whole liver objective response rate, $P = .823$ for whole liver disease control rate, $P = .558$ for treated lesion objective response rate, $P = .652$ for treated lesion disease control rate).

differences between response in the conventional TACE, DEBDOX, and hqTACE high-risk groups (Fig 3).

In the total study cohort, response and disease control rates were higher for first-time treatments of previously treatment-naive patients (Fig 4). However, whole liver and treated lesion response rates were still over 50% in previously treated patients, including patients who had undergone up to seven previous TACE procedures.

Discussion

Critical shortages of drugs in the United States have required the medical system to adapt and to improvise (15). For the HCC community, the abrupt and unexplained withdrawal of Ethiodol from the market and the interruption in supply of lyophilized doxorubicin and cisplatin disrupted the care of thousands of patients. New drug-eluting microsphere technologies have emerged to fill the need. These calibrated, round microspheres contain anionic moieties (sulfonates, carboxyl groups) that interact with positively charged moieties in drugs such as doxorubicin by an ion-exchange mechanism and allow loading of the drug from dilute solutions. Use of drug-eluting microspheres for TACE leads to high and sustained intratumoral doxorubicin concentrations, as well as decreased systemic drug levels and toxicity (3–8).

Previous studies have shown similar outcomes for embolotherapy for HCC regardless of which delivery vehicles and chemotherapeutic agents (if any) were used (3). Subtle differences have been found for specific patient groups, such as those with compromised liver function or performance status in the PRECISION V trial (8). Another single-center retrospective study revealed superior overall response and disease control using DEBDOX or three-drug conventional TACE compared with single-drug doxorubicin conventional TACE (16). In contradistinction, our study and that of Sacco et al (17) show at least equivalence of conventional TACE, supporting its continued wide use, especially for superselective treatment and/or in situations where the cost of materials dictates usage. The much smaller total amount of drug used in our study compared with that in the PRECISION V trial (142 vs 75 mg) for nearly the same tumor load and angiographic end point suggests that our physicians practiced greater catheter selectivity than did the PRECISION V physicians.

Maximally selective catheterization is associated with lower toxicity, greater tumor necrosis, and prolonged survival (18–20). Our study, a result of involuntary protocol adaptations due to drug shortages, showed that the differences between conventional TACE, DEBDOX TACE, and hqTACE are negligible when used with maximal catheter selectivity. No clinically significant differences in overall toxicity and response were found. In fact, trends were found favoring conventional TACE with less symptoms of postembolization syndrome, lower increase in Child-Pugh score, and lower increase in alkaline phosphatase, suggesting the possibility of less biliary toxicity. Specifically, the advantages of higher response rates in high-risk patients, lower hepatic and

Figure 4

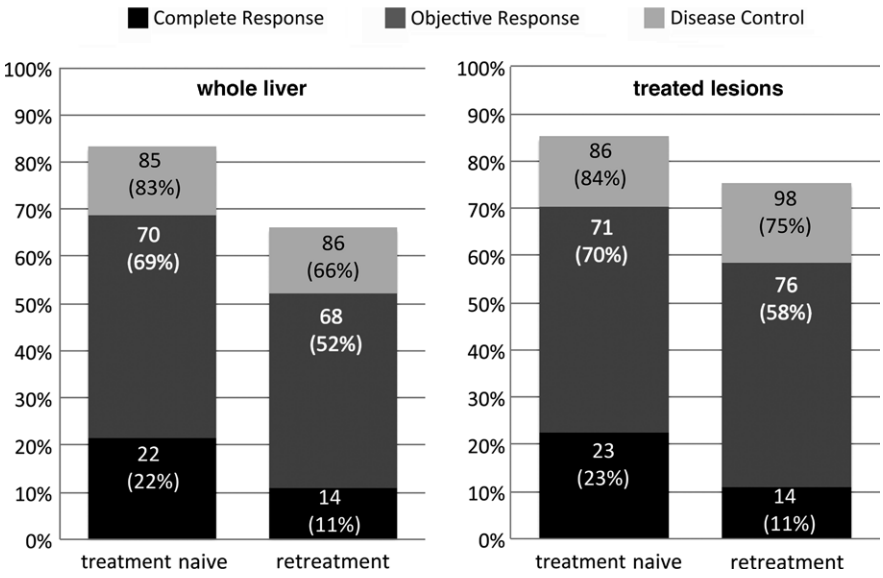

Figure 4: Response to first-time treatment in treatment-naive patients versus retreatment. Whole liver objective response (Mann Whitney *U* test $P = .012$) and disease control ($P = .003$) were significantly higher in first-time treatments compared with retreatments, but only trends were seen for treated lesion objective response and disease control ($P = .056$ and .062).

systemic toxicity, and fewer treatment-related and treatment-emergent adverse events using drug-eluting microspheres reported in the PRECISION V trial were not duplicated in our study. Our total number of high-risk patients (n = 121) was similar to that in PRECISION V trial (n = 135), but distributed more heavily into the conventional TACE group.

Our patient cohort had a slightly lower tumor burden than did the subjects of PRECISION V trial. This may have allowed more superselective treatment, which likely obscured the advantages reported in PRECISION V trial. This may also partly explain our 15%–43% higher response and disease control rates when compared with the PRECISION V results (19). In addition, we found that response rates in the low-risk groups were superior to those in the high-risk group for conventional TACE and DEBDOX TACE, a finding different from what was found in PRECISION V trial, also likely due to greater catheter selectivity and smaller tumor load in our patients. Our use of C-arm cone-beam CT on every patient to document complete tumor uptake may have been another factor (9,10). Superselective catheterization and use of C-arm CT typically require additional procedure time and radiation exposure, and our procedure times averaged approximately 100 minutes. Superselectivity also raises the risk of incomplete treatment, and our complete response rates were in fact lower than the PRECISION V statistics, but their rates were reported after three treatments and ours after only a single treatment. Incomplete superselective treatment of larger tumors may also partially explain the trend toward lower response rates in our hqTACE group, who had a slightly larger initial tumor load than did the other two groups. The majority of our procedures were re-treatments of patients previously treated with TACE who had residual or recurrent disease, and the favorable response rates support the findings of other investigators that repeat superselective TACE results in substantial response rates, although not quite as high as with treatment-naive patients (21).

A few other differences were observed between the vehicles. The total drug dose delivered was highest for LC Beads, mostly due to formulation protocols, but this was not accompanied by greater doxorubicin-related toxicity. Since the period of this study, manufacturer's recommendations for QuadraSpheres preparation have been revised upward to 75 mg doxorubicin per vial, which will probably eliminate this difference. Other differences included the need for gentler handling of QuadraSpheres to prevent fragmentation, the difference in stasis end point for QuadraSpheres and a slightly longer median procedure time (not significant), and the risk of spillage from degradation of syringes and stopcocks by Ethiodol. The cost of the materials ranged from $238 per 10-mL vial of Ethiodol to $1443 per vial of QuadraSpheres and $1531 per vial of LC Beads.

The limitations of our study include the relatively small number of patients in each group, especially in the hqTACE group, the retrospective nature, the short period of follow-up, the different chemotherapeutic regimens used, and the lack of true randomization. To detect a 10% difference between treatment groups at 80% power would have required enrollment of 840 patients (280 each); with our actual numbers, only a difference of 23% between conventional TACE and DEBDOX TACE, of 28% between conventional TACE and hqTACE, and of 33% between DEBDOX and hqTACE could have been detected at 80% power. Six treating physicians with different styles contributed cases to this series. Different learning curves, especially for hqTACE, which requires extra time and effort to achieve the recurrent stasis end point, may have contributed to some of the subtle differences in outcomes. All patients with residual or recurrent disease went on to further TACE treatment, sometimes by a different TACE vehicle depending again on availability, limiting the value of longer term data. Cardiac toxicity was not measured, but no clinical evidence of heart failure was encountered. Clinical toxicities were almost all self-reported and were probably underrepresented.

In conclusion, doxorubicin-delivering LC Beads, QuadraSpheres, and

ethiodized oil emulsions appear to be equivalent in efficacy and toxicity when used for superselective TACE with C-arm CT guidance in HCC patients. Meticulous, superselective catheterization may diminish or nullify the advantages of using drug-eluting microspheres, even in high-risk patients, by increasing efficacy and limiting toxicity.

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