

## Precision Hepatic Arterial Irinotecan Therapy in the Treatment of Unresectable Intrahepatic Cholangiocellular Carcinoma: Optimal Tolerance and Prolonged Overall Survival

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### ABSTRACT

**Background.** Unresectable intrahepatic cholangiocellular carcinoma (ICC) carries a poor prognosis, and there are few chemotherapeutic treatments to prolong survival. The purpose of this study was to assess the efficacy of drug-eluting bead (DEB) therapy by transarterial infusion for unresectable ICC.

**Methods.** A prospective multicenter study of ICC patients who received hepatic arterial DEB therapy.

**Results.** Twenty-four patients with unresectable ICC were treated with DEB. Ten patients (41.6%) had recurrent ICC after prior radiofrequency ablation ( $n = 3$ ) or hepatectomy ( $n = 7$ ). Twenty patients (80%) had received prior chemotherapy, mostly of gemcitabine ( $n = 8$ ) or Eloxatin ( $n = 6$ ). The percent of overall liver involvement was  $< 25\%$  ( $n = 8$ ), 26% to 50% ( $n = 11$ ), and  $> 50\%$  ( $n = 4$ ). Ten patients (40%) had sites of extrahepatic disease located at lymph nodes ( $n = 5$ ), bone ( $n = 2$ ), peritoneum ( $n = 1$ ), lung ( $n = 1$ ), and mouth ( $n = 1$ ). A total of 42 DEB treatments were administered. Eight were administered in combination with systemic chemotherapy of FOLFOX ( $n = 4$ ) or Gemzar ( $n = 4$ ). Twelve patients (48%) received a second treatment, and 4 patients (16%) received a third treatment. The median length of stay was

23 h (23–72 h). Eleven adverse reactions (26.2%) were reported. Of these, 7 (63.6%) were minor (less than grade 3). One patient died from hepatorenal syndrome. The disease of one patient was downstaged to resection. After a median follow-up of 13.6 months, the median overall survival of a multitherapeutic regimen with DEB therapy was significantly greater than chemotherapy alone (17.5 vs. 7.4 months;  $P = 0.02$ ).

**Conclusions.** Bead therapy is safe and effective in patients with unresectable ICC. There is a marked survival benefit when DEB therapy is used as adjunctive therapy.

Intrahepatic cholangiocellular carcinoma (ICC) is a malignant tumor arising from the epithelial cells lining the biliary tree within the liver parenchyma. The incidence has been increasing over the past 30 years, and now these tumors account for approximately 10% to 15% of all primary hepatic tumors.<sup>1</sup> Patients typically present with advanced-stage disease, resulting in a low resectability rate and poor prognosis. The presence of multiple tumors, large tumor size, poor differentiation, vascular invasion, and lymph node metastases has been associated with poor survival.<sup>2,3</sup> The 5-year survival rate ranges from 5% to 42%, and there are few long-term survivors.<sup>4–6</sup>

Tumor resection is the only potential for long-term survival, and patients require partial hepatectomy to increase the chances of obtaining a negative resection margin.<sup>3,7,8</sup> Approximately 75% of patients had unresectable disease at the time of presentation.<sup>9</sup> The major determinants of resectability are the extent of tumor within

the biliary tree, the amount of hepatic parenchyma involved, vascular invasion, hepatic lobar atrophy, biliary tract involvement, and metastatic disease.<sup>10,11</sup> Approximately 16% to 25% of patients are found to have unresectable disease at the time of laparotomy, most commonly from peritoneal metastatic disease.<sup>12</sup> Furthermore, many patients develop recurrent disease after surgical resection.<sup>13,14</sup> Even when surgery is successfully performed, the 5-year survival rate remains 20% to 40%.<sup>6,15,16</sup> The roles of adjuvant radiotherapy or chemotherapy after hepatectomy remain controversial, given the limited effect these additional therapies have played in improving overall survival.<sup>17–20</sup>

Unresectable ICC carries a poor prognosis, with a median survival time of 6 to 12 months, and currently there are no established chemotherapeutic treatments to prolong survival.<sup>17,21</sup> Palliative radiotherapy has shown minimal benefit in the treatment of unresectable ICC. The optimal management strategy for unresectable ICC remains to be defined, and new regimens are needed to prolong survival and increase response rates.

ICCs are predominantly supplied by the branches of the hepatic arterial system, making these malignancies amenable to hepatic arterial chemotherapy. Hepatic arterial therapy delivers chemotherapeutic agents directly to the tumor. Approximately 85% of the drug is metabolized in the liver, thus limiting systemic side effects. This therapy can induce tumor ischemia and promotes long-lasting intratumoral retention of chemotherapeutic agents. Drug-eluting bead (DEB) therapy represents a new and innovative delivery device that can deposit chemotherapeutic agents with minimal release into adjacent tissues. The beads are delivered as an outpatient therapy, and recent reports have shown that DEB therapy is well tolerated.<sup>22–27</sup> DEBs may increase the intensity and duration of ischemia and enhance delivery of chemotherapeutic agents.<sup>28</sup> The aim of this study was to assess the efficacy of DEB therapy by hepatic transarterial infusion in combination with systemic therapy in the treatment of unresectable ICC.

## METHODS

This study was a prospective, multi-institutional review of the International Bead Registry of patients with unresectable ICC who received hepatic arterial DEB therapy. The registry received institutional review board approval and complied with the principles and protocols laid down in the Declaration of Helsinki in accordance with the International Conference of Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice.<sup>29</sup>

Consecutive patients with unresectable ICC were included, and patients with extrahepatic cholangiocarcinomas

(hilar and Klatskin tumors) were excluded. Inclusion criteria for chemoembolization with hepatic arterial DEB therapy were as follows: (1) confirmed diagnosis of ICC by tissue biopsy; (2) Karnofsky performance score of 60% to 100%; (3) age  $\geq 18$  years; and (4) patient able to provide informed consent in accordance with institutional and national guidelines. Exclusion criteria were as follows: (1) history of severe allergy or intolerance to contrast media; (2) bleeding diathesis; (3) severe peripheral vascular disease precluding catheterization; (4) clinically important extrahepatic disease, generally in excess of 50% of the overall whole body tumor bulk, or any tumor burden that represented an imminent threat to the patient's life; (5)  $>75\%$  hepatic parenchymal involvement; (6) severe liver dysfunction; (7) active, uncontrolled infection; or (8) any other contraindication to hepatic angiography and selective visceral catheterization.<sup>26</sup>

Intra-angiographic assessment is the gold standard for use of hepatic arterial therapy. Hepatic arterial therapy usage is not based on the vascularity seen in computed tomographic (CT) arterial phase images because there is wide variation in the timing of the arterial phase images obtained. Thus, because it is well established that all cancers of the liver and biliary tract derive most their blood supply from the arterial system, we have used angiography as the final determinant for treatment. Our prior studies have demonstrated the safety and efficacy of treating hypovascular lesions seen on CT scan.<sup>26,30</sup>

DEBs loaded with irinotecan (DEBIRI) are delivered to the tumor by transarterial chemoembolization (TACE). The primary functions of the device are to embolize the small arteries feeding the tumor, thus causing hypoxia, and to deliver irinotecan to the tumor in a controlled manner. Drug-eluting beads loaded with doxorubicin (DEBDOX) were also used in this study when irinotecan was not available or at the physician's discretion. Treatment was performed via a lobar approach on the basis of the extent and distribution of the disease. The method of DC/LC Bead therapy has been described previously.<sup>30</sup> The drug-eluting bead (DEBIRI or DEBDOX) used in this report is the DC/LC Bead (Biocompatibles, Farnham, UK), which is a PVA microsphere with U.S. Food and Drug Administration clearance as a class II device. It is also CE marked as a drug delivery embolization system. The beads are available in the size ranges of 100 to 300  $\mu\text{m}$ , 300 to 500  $\mu\text{m}$ , 500 to 700  $\mu\text{m}$ , and 700 to 900  $\mu\text{m}$ . The size of bead used in each treatment was at the discretion of the treating physician.

Follow-up assessments included a triphase CT scan of the liver within 3 months of treatment. Evaluation of the enhancement pattern of the target lesion and tumor response rates was measured according to Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST

criteria.<sup>31–35</sup> The diameter of the hypervascular portion of the tumor was evaluated at baseline and during follow-up.

Adverse events defined as an untoward deviation in health away from baseline due to any cause were recorded during the hospital stay and for 30 days after each treatment and were graded according to the standard 5-point grading scale. All adverse events were recorded per standards and terminology set forth by the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, version 3.0. Major complications were defined as grade 3 or higher. Postembolization syndrome was defined as nausea, emesis and abdominal discomfort.

Data entry was monitored for completeness and accuracy at University of Louisville. A central assessment of tumor response was performed for all patients by the principal investigator at University of Louisville. Data analysis was limited to descriptive reports of the number and characteristics of the patients treated, and their clinical responses and adverse events.

Patients undergoing hepatic arterial DEBIRI or DEB-DOX therapy were compared to reported outcomes in the literature of patients who were treated with systemic chemotherapy only. Literature regarding systemic chemotherapy use in the treatment of unresectable ICC was identified by a review of all publications in peer-reviewed journals in the English language from 1995 to 2008. Unpublished studies and abstracts presented at national and international meetings were not included. Publications were identified by conducting a comprehensive search of Medline, Embase, Science Citation Index, Current Contents, and PubMed databases, with medical subject headings of “intrahepatic cholangiocarcinoma,” “cholangiocarcinoma,” “chemotherapy,” and “bile duct cancers.” A manual search of the abstracts was performed to identify publications for inclusion in this review. Case reports, articles in which systemic chemotherapy was combined with additional radiotherapy or TACE, and studies that did not differentiate biliary tract cancers by location were discarded.

Statistical analysis was performed by JMP 4.0 and SPSS version 16 software (SPSS, Chicago, IL). Survival was plotted by the Kaplan–Meier method and compared by the log rank test. Survival (in months) was measured from date of initial diagnosis until death or last follow-up visit.

## RESULTS

Twenty-four patients with a diagnosis of unresectable ICC underwent hepatic arterial DEB therapy. There were 9 men (37.5%) and 15 women (62.5%). The median age at diagnosis was 59 years, with a range of 33 to 80 years (Table 1). The median height was  $1.7 \pm 0.2$  m. The

**TABLE 1** Demographic data and tumor characteristics of 24 patients

Characteristic	Value
Median age (y) (range)	59 (33–80)
Sex (M, F)	9, 15
Tobacco use	24%
Ethyl alcohol consumption	0%
Prior surgery	7
Right hepatectomy	4
Right trisegmentectomy	1
Left hepatectomy	1
Caudate lobectomy	1
Prior radiofrequency ablation	3
Prior chemotherapy	
Gemcitabine	7
Oxaliplatin $\pm$ bevacizumab	4
FOLFOX	1
Other	2
Karnofsky score	
100%	9
90%	6
80%	6
<80%	1
Height (m)	
Median	1.7
Mean	1.7
Standard deviation	0.2
Weight (kg)	
Median	70
Mean	71.2
Standard deviation	14.3
Basal metabolic index (kg/m <sup>2</sup> )	
Median	25.5
Mean	25.8
Standard deviation	5.9
Race	
White	22
African American	2
Liver lesion distribution	
Distinct number	11
Numerous	13
Median no. of total lesions (range)	3 (1–25)
No. of tumors	
1	3
2–3	5
>3	16
Liver involvement	
<25%	9
26%–50%	11
>50%	4

**TABLE 1** continued

Characteristic	Value
Median target lesion size (cm) (range)	11.5 (4–33.3)
Median no. of target lesions (range)	2 (1–5)
Site of extrahepatic disease	10
Lymph nodes	5
Bone	2
Peritoneum	1
Lung	1
Mouth	1

median weight was  $70 \pm 14.3$  kg. The median basal metabolic index was  $25.5 \pm 5.9$  kg/m<sup>2</sup>. Twenty-four percent of the patients used tobacco, and none reported alcohol use. Medical histories included cardiac disease, pulmonary disease, diabetes, and hypertension. None of the patients in this study had cirrhosis, either by pathological (patients with prior resection) or radiological (patients with unresectable disease at initial presentation) diagnosis.

Seven patients (29.2%) had recurrent ICC after prior hepatic resection. Of these, right hepatectomy ( $n = 4$  patients) was the most common, followed by right trisegmentectomy ( $n = 1$ ), left hepatectomy ( $n = 1$ ), and caudate resection ( $n = 1$ ). Three patients had recurrent ICC after prior radiofrequency ablation (RFA). Twenty patients (80%) had received prior chemotherapy, mostly of gemcitabine ( $n = 8$ ) or Eloxatin ( $n = 6$ ).

The extent of liver disease was defined as innumerable liver lesions in 13 (54.2%), and 11 (45.8%) had a distinct number of lesions (Table 1). The median number of liver lesions was 3 but ranged from 1 to 25 lesions. Overall liver involvement was <25% ( $n = 9$ ), 26% to 50% ( $n = 11$ ), and >50% ( $n = 4$ ). The median size of the target lesion was 11.5 cm (range, 4–33.3 cm). Ten patients (41.7%) had sites of extrahepatic disease located at the lymph nodes ( $n = 5$ ), bone ( $n = 2$ ), peritoneum ( $n = 1$ ), lung ( $n = 1$ ), and mouth ( $n = 1$ ).

A total of 42 DEB treatments were administered; 35 treatments (83.3%) used irinotecan and 7 (16.7%) used doxorubicin. The median dosage delivered for irinotecan was 75 mg (range, 40–100 mg), and the median dosage for doxorubicin was 150 mg (range, 150–150 mg). Twelve patients (50%) underwent a single bead treatment, 8 patients (33.3%) received two treatments, and 4 patients (16.7%) underwent three treatments. The locations treated were right (51%), left (43%), and middle (5%) hepatic arteries. The technical success rate was 100%. The degree of flow occlusion was complete (46%), near complete (33%), and partial (21%) (Table 2).

The median length of stay was 23 h (range, 23–72 h). Of the 42 treatment sessions, 11 (26.2%) adverse events

**TABLE 2** Details of irinotecan-based bead treatments

Characteristic	Value
No. of bead courses	
1	12
2	8
3	4
Treatment location	
Right	51%
Left	43%
Middle	5%
Level of branching	
Lobar	88%
Segmental	6%
Subsegmental	6%
Drug provided	
Irinotecan	35
Doxorubicin	7
Median dose delivered (mg) (range)	
Irinotecan	75 (40–100)
Doxorubicin	150 (150–150)
Bead size ( $\mu$ m)	
100–300	71%
300–500	17%
500–700	2%
100–300, then 300–500	10%
Degree of occlusion	
Complete	46%
Near	33%
Partial	21%
Technical success	100%
Concurrent chemotherapy	
FOLFOX $\pm$ bevacizumab	3
Other	5

were reported. Of these, 7 (63.6%) were minor (less than grade 3) and 4 (36.3%) were major (grade 3 or higher). Four patients (40%) developed postembolization syndrome that was either grade 1 or grade 2 in severity. One patient died from hepatorenal syndrome. This patient had numerous lesions in the right side of his liver with approximately 51% to 75% liver involvement. An 11-cm lesion in segment V was treated with one DEB course with 100 mg of irinotecan. He had not undergone prior chemotherapeutic treatment, hepatic resection, or radiofrequency ablation. Preoperative total bilirubin was 1.6 mg/dl, and preoperative creatinine was 1.3 mg/dl. The patient died 12 days after DEB treatment. Other treatment-related adverse events included 1 patient who developed sepsis from a port infection (grade 4), 2 patients with atrial fibrillation (grade 2), and 1 patient with pneumonia (grade 2). Two patients

developed hepatic insufficiency (grade 3) that was self-limited and resolved (Table 3).

Response rate data were recorded at 3 months, 6 months, and 9 to 12 months (Table 4). At 3 months, the tumor response rate (complete response + partial response) was 79% by modified RECIST and 8% by RECIST criteria. RECIST criteria misclassify many patients with a partial response as having stable disease because it

**TABLE 3** Type and incidence of adverse events

Complication	Grade	<i>n</i>
Postembolization syndrome	1 to 2	4
Pneumonia	2	1
Atrial fibrillation	2	2
Hepatic insufficiency	3	2
Sepsis	4	1
Hepatorenal death	5	1

**TABLE 4** Tumor response for initial follow-up visit at various time points

Response	3 months	6 months	9–12 months
<b>RECIST</b>			
CR	1 (4%)	2 (10%)	1 (6%)
PR	1 (4%)	3 (15%)	1 (6%)
SD	20 (83%)	13 (65%)	13 (72%)
PD	2 (8%)	2 (10%)	3 (17%)
<b>Modified RECIST</b>			
CR	1 (4%)	2 (10%)	1 (6%)
PR	18 (75%)	14 (70%)	12 (67%)
SD	3 (13%)	2 (10%)	2 (11%)
PD	2 (8%)	2 (10%)	3 (17%)

RECIST Response Evaluation Criteria in Solid Tumors, CR complete response, PR partial response, SD stable disease, PD progressive disease

does not take tumor necrosis into account and vastly underestimates tumor response.<sup>33,34</sup> Two patients (8%) had progressive disease at 3 months. At 6 months, the tumor response rate was 80% by modified RECIST and 25% by RECIST criteria, and an additional 3 patients (15%) demonstrated progressive disease. At 9- to 12-month follow-up assessment, the tumor response rate was 73% by modified RECIST and 12% by RECIST criteria, with an additional 3 patients (17%) demonstrating progressive disease.

Three patients were downstaged to resection and underwent subsequent hepatectomy with radiofrequency ablation. Three patients showed a complete response with 100% loss of positron emission tomography scan activity. Of these, 1 patient remains free of disease (follow-up time, 33.8 months) and 2 patients are alive with disease (follow-up time, 33.3 and 80 months).

The median follow-up time was 13.6 months. The median overall survival of a multitherapeutic regimen with DEB therapy was 17.5 months, as compared to chemotherapy alone, which was 7.4 months in the literature review ( $P = 0.02$ ) (Table 5; Fig. 1).

## DISCUSSION

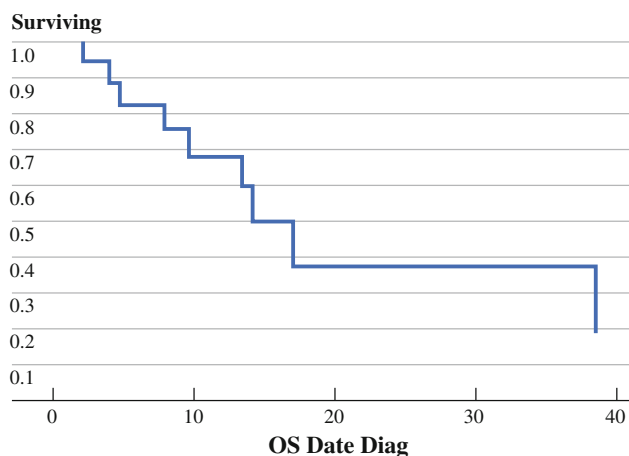
Unresectable ICC carries a poor prognosis, and currently there are no established chemotherapeutic protocols to prolong survival. Patients generally present with advanced-stage disease that is not amenable to surgical resection. The multidisciplinary treatment strategy for unresectable ICC is becoming more complex, and the optimal management strategy remains to be defined. Our results demonstrated that precision hepatic arterial therapy with DEBIRI or DEBDOX is safe and effective. DEB therapy achieved major tumor necrosis while minimizing systemic exposure to chemotherapeutic agents, thus reducing side effects.

There are no standardized recommendations for systemic chemotherapy in unresectable ICC. Treatment with

**TABLE 5** Current literature of reported effectiveness of systemic chemotherapy in the treatment of unresectable intrahepatic cholangiocellular carcinoma

Study	No. of patients	Type of chemotherapy	Response rate (%)	Adverse events	Overall survival (mo)
Feisthammel et al. <sup>54</sup> (2007)	17	Irinotecan + 5-FU	5.9	Sepsis (death), hematologic, GI	5.5
Kim et al. <sup>38</sup> (2008)	38	Gemcitabine ± platinum	16.7	NR	7.6
Kim et al. <sup>38</sup> (2008)	54	Fluoropyrimidines ± platinum	19.5	NR	7.6
Lee et al. <sup>55</sup> (2004)	20	Epirubicin, cisplatin, + 5-FU	10	Hematologic	5
Nehls et al. <sup>56</sup> (2008)	18	Capecitabine + oxaliplatin	0	Hematologic, GI, thromboembolic	5.2
Sasaki et al. <sup>57</sup> (2009)	14	Gemcitabine + S-1	28.6	Hematologic	10.3
Takezako et al. <sup>58</sup> (2008)	39	Cisplatin, epirubicin + 5-FU	10	Sepsis (2 deaths), hematologic, GI	9.1

5-FU 5-fluorouracil, GI gastrointestinal, NR not recorded



**FIG. 1** Kaplan–Meier survival curve depicting overall survival of patients ( $N = 24$ ) with unresectable intrahepatic cholangiocellular carcinoma treated with transarterial chemoembolization–drug-eluting beads loaded with irinotecan or transarterial chemoembolization–drug-eluting beads loaded with doxorubicin therapy

5-fluorouracil (5-FU) has approximately a 10% to 15% response rate when provided alone.<sup>3</sup> Combination chemotherapy with 5-FU showed response rates between 15 and 55% and a median survival rate of 6 to 12 months.<sup>7,36–41</sup> An initial phase 2 study of systemic irinotecan found a partial response rate of 8% and stable disease in 40% of participants, and the median survival was 10 to 12 months.<sup>36</sup> Gemcitabine showed a 30% response rate when used as a single agent.<sup>40,42–44</sup> Gemcitabine combined with a platinum compound yielded a 30% to 50% response rate and 10- to 15-month survival.<sup>17,40,42–44</sup> Most studies about systemic chemotherapy administration for unresectable ICC do not stratify response rates and overall survival by location of the pathology. We found six studies that differentiated ICC from other biliary tract cancers. These studies reported response rates of 5.9% to 30% and overall survival from 5 to 10.3 months (Table 5).

Treatment with radiotherapy has shown little benefit in prolonging survival. Zeng et al. reported an objective response rate of 36.4% to external beam radiation and showed prolonged survival.<sup>45</sup> Radioembolization with yttrium-90 microspheres showed a median survival of 20.4 months; however, most of these patients received concurrent chemotherapy, and 40% had undergone prior liver resection.<sup>21</sup> Additionally, this technique may not be available at all treatment centers.

TACE combines hepatic artery embolization with infusion of concentrated doses of chemotherapeutic agent directly into the tumor. The development of DEBs loaded with chemotherapy and delivered by TACE may increase the intensity and duration of ischemia while enhancing drug delivery. DEBs slowly release chemotherapy when injected and decrease the passage of drugs into systemic

circulation, even when high doses are administered. These functions enhance the toxic effect of the drug while minimizing systemic side effects. DEB therapy is a more precision-directed device as compared to prior hepatic arterial therapies. TACE with DEBIRI has been used in the multidisciplinary treatment of hepatocellular carcinoma and liver metastases from colorectal cancer, ocular melanoma, and neuroendocrine tumors with promising results and minimal adverse effects.<sup>23–28,30,46–49</sup>

In the current study, patients with unresectable ICC were treated by TACE with DEBIRI or DEBDOX, and the tumor response criteria were determined by both RECIST and modified RECIST criteria. RECIST criteria do not account for the degree of tumor necrosis and may underestimate tumor response because necrosis is not paralleled by reduction in tumor diameter.<sup>33,34</sup> The conclusions from the Barcelona-2000 EASL conference recommended that estimations of tumor response include tumor necrosis, which can be estimated by areas by nonenhancement of contrast CT scan or magnetic resonance imaging.<sup>33</sup> In the current study, RECIST criteria vastly underestimated a partial tumor response and instead categorized many of these patients as having stable disease.

The response rates in the current study exceeded the rates reported with traditional TACE therapy, which are 30% to 40%.<sup>50–52</sup> The current study yielded response rates between 70% and 80%, with an additional 5% to 13% of patients having stable disease. Cantore et al. performed a phase 2 trial evaluating the efficacy of combined locoregional and systemic chemotherapy. Thirty consecutive patients with advanced biliary tract tumors were treated with hepatic intra-arterial infusion of epirubicin and cisplatin and concurrent systemic 5-FU. The overall response rate was 40%, with an additional 40% having stable disease. The median overall survival was 13 months.<sup>50</sup> Mambrini et al. treated 20 patients with intra-arterial infusion of epirubicin and cisplatin combined with capecitabine. They showed 31.5% response rate and stable disease in 47.5% with an overall survival of 18 months.<sup>53</sup>

The median overall survival of a multitherapeutic regimen with DEBIRI was significantly longer than chemotherapy alone (17.5 vs. 7.4 months,  $P = 0.02$ ). Response rates with combination chemotherapy ranged from 15% to 55%, with median overall survival ranging from 5 to 10.3 months in the recent literature.<sup>17,38,39,43,44,50</sup> The addition of TACE with DEBIRI to multidisciplinary treatment regimen greatly prolonged survival and increased the tumor response and control rates.

The most common adverse effect was postembolization syndrome of either grade 1 or 2 severity and was present in 4 patients (16.7%). Pretreatment with intra-arterial 1% plain lidocaine has led to effective amelioration of peri-procedural discomfort in most patients.<sup>23,31</sup> There were no

device-related complications or complications related to hepatic artery cannulation. None of the patients displayed adverse events consistent with systemic administration of irinotecan.

A weakness of this study was that this was not a randomized, controlled trial. The data were prospectively collected and retrospectively analyzed. The data obtained were compared to historical data regarding systemic chemotherapy. The patients did not receive identical treatments at all of the participating sites.

In conclusion, the use of TACE with DEBIRI or DEBDOX was safe and effective in the treatment of unresectable ICC as demonstrated by the low complication rate and by tumor response criteria. Patients exhibited much longer overall survival time as compared to patients treated with chemotherapy only. Results of this study warrant further prospective investigations in the form of controlled clinical trials to confirm this data and to establish the role of hepatic transarterial chemotherapy with DEBIRI in the multidisciplinary treatment strategy of unresectable ICC.

## REFERENCES

1. Shaib YH, El-Serag HB, Davila JA, Morgan R, McGlynn KA. Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. *Gastroenterology*. 2005;128:620–6.
2. Choi SB, Kim KS, Choi JY, et al. The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. *Ann Surg Oncol*. 2009;16:3048–56.
3. Aljiffry M, Walsh MJ, Molinari M. Advances in diagnosis, treatment and palliation of cholangiocarcinoma: 1990–2009. *World J Gastroenterol*. 2009;15:4240–62.
4. Shaib YH, El-Serag HB, Nooka AK, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a hospital-based case-control study. *Am J Gastroenterol*. 2007;102:1016–21.
5. Lim JH. Cholangiocarcinoma: morphologic classification according to growth pattern and imaging findings. *AJR Am J Roentgenol*. 2003;181:819–27.
6. Jan YY, Yeh CN, Yeh TS, Hwang TL, Chen MF. Clinicopathological factors predicting long-term overall survival after hepatectomy for peripheral cholangiocarcinoma. *World J Surg*. 2005;29:894–8.
7. Choi CW, Choi IK, Seo JH, et al. Effects of 5-fluorouracil and leucovorin in the treatment of pancreatic-biliary tract adenocarcinomas. *Am J Clin Oncol*. 2000;23:425–8.
8. Rocha FG, Matsuo K, Blumgart LH, Jarnagin WR. Hilar cholangiocarcinoma: the Memorial Sloan-Kettering Cancer Center experience. *J Hepatobiliary Pancreat Surg*. (in press).
9. Tan JC, Coburn NG, Baxter NN, Kiss A, Law CH. Surgical management of intrahepatic cholangiocarcinoma: a population-based study. *Ann Surg Oncol*. 2008;15:600–8.
10. Jarnagin WR, Fong Y, Dematteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg*. 2001;234:507–17.
11. Yang J, Yan LN. Current status of intrahepatic cholangiocarcinoma. *World J Gastroenterol*. 2008;14:6289–97.
12. Nakeeb A, Pitt HA, Sohn TA, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg*. 1996;224:463–73.
13. Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg*. 2008;248:84–96.
14. Khan SA, Davidson BR, Goldin R, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. *Gut*. 2002;51(Suppl 6):VI1–VI9.
15. Yamamoto M, Takasaki K, Otsubo T, Katsuragawa H, Katagiri S. Recurrence after surgical resection of intrahepatic cholangiocarcinoma. *J Hepatobiliary Pancreat Surg*. 2001;8:154–7.
16. Weber SM, Jarnagin WR, Klimstra D, et al. Intrahepatic cholangiocarcinoma: resectability, recurrence pattern, and outcomes. *J Am Coll Surg*. 2001;193:384–91.
17. Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. *Br J Cancer*. 2007;96:896–902.
18. Thongprasert S. The role of chemotherapy in cholangiocarcinoma. *Ann Oncol*. 2005;16(2):93–96.
19. Todoroki T. Chemotherapy for bile duct carcinoma in the light of adjuvant chemotherapy to surgery. *Hepatogastroenterology*. 2000;47:644–9.
20. Gerhards MF, Van Gulik TM, Gonzalez GD, Rauws EA, Gouma DJ. Results of postoperative radiotherapy for resectable hilar cholangiocarcinoma. *World J Surg*. 2003;27:173–9.
21. Saxena A, Bester L, Chua TC, Chu FC, Morris DL, Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. *Ann Surg Oncol*. (in press).
22. Fiorentini G, Aliberti C, Benea G, et al. TACE of liver metastases from colorectal cancer adopting irinotecan-eluting beads: beneficial effect of palliative intra-arterial lidocaine and post-procedure supportive therapy on the control of side effects. *Hepatogastroenterology*. 2008;55:2077–82.
23. Fiorentini G, Aliberti C, Del CA, et al. Intra-arterial hepatic chemoembolization (TACE) of liver metastases from ocular melanoma with slow-release irinotecan-eluting beads. Early results of a phase II clinical study. *In Vivo* 2009;23:131–7.
24. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol*. (in press).
25. Malagari K. Drug-eluting particles in the treatment of HCC: chemoembolization with doxorubicin-loaded DC Bead. *Expert Rev Anticancer Ther*. 2008;8:1643–50.
26. Martin RC, Robbins K, Tomalty D, et al. Transarterial chemoembolization (TACE) using irinotecan-loaded beads for the treatment of unresectable metastases to the liver in patients with colorectal cancer: an interim report. *World J Surg Oncol*. 2009;7:80.
27. Aliberti C, Tilli M, Benea G, Fiorentini G. Trans-arterial chemoembolization (TACE) of liver metastases from colorectal cancer using irinotecan-eluting beads: preliminary results. *Anticancer Res*. 2006;26:3793–5.
28. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol*. 2007;46:474–81.
29. Levine MN, Julian JA. Registries that show efficacy: good, but not good enough. *J Clin Oncol*. 2008;26:5316–9.
30. Martin RC, Joshi J, Robbins K, Tomalty D, O'Hara R, Tatum C. Transarterial chemoembolization of metastatic colorectal carcinoma with drug-eluting beads, irinotecan (DEBIRI): multi-institutional registry. *J Oncol*. (in press).
31. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European

- Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92:205–16.
32. Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. *Eur J Cancer.* 2006;42:1031–9.
  33. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol.* 2001;35:421–30.
  34. Forner A, Ayuso C, Varela M, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? *Cancer.* 2009;115:616–23.
  35. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228–47.
  36. Sanz-Altamira PM, O'Reilly E, Stuart KE, et al. A phase II trial of irinotecan (CPT-11) for unresectable biliary tree carcinoma. *Ann Oncol.* 2001;12:501–4.
  37. Ducreux M, Van CE, Van Laethem JL, et al. A randomised phase II trial of weekly high-dose 5-fluorouracil with and without folinic acid and cisplatin in patients with advanced biliary tract carcinoma: results of the 40955 EORTC trial. *Eur J Cancer.* 2005;41:398–403.
  38. Kim MJ, Oh DY, Lee SH, et al. Gemcitabine-based versus fluoropyrimidine-based chemotherapy with or without platinum in unresectable biliary tract cancer: a retrospective study. *BMC Cancer.* 2008;8:374.
  39. Rao S, Cunningham D, Hawkins RE, et al. Phase III study of 5FU, etoposide and leucovorin (FELV) compared to epirubicin, cisplatin and 5FU (ECF) in previously untreated patients with advanced biliary cancer. *Br J Cancer.* 2005;92:1650–4.
  40. Knox JJ, Hedley D, Oza A, et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. *J Clin Oncol.* 2005;23:2332–8.
  41. Knox JJ, Hedley D, Oza A, et al. Gemcitabine concurrent with continuous infusional 5-fluorouracil in advanced biliary cancers: a review of the Princess Margaret Hospital experience. *Ann Oncol.* 2004;15:770–4.
  42. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.* 2010;362:1273–81.
  43. Lee GW, Kang JH, Kim HG, et al. Combination chemotherapy with gemcitabine and cisplatin as first-line treatment for immunohistochemically proven cholangiocarcinoma. *Am J Clin Oncol.* 2006;29:127–31.
  44. Kim ST, Park JO, Lee J, et al. A Phase II study of gemcitabine and cisplatin in advanced biliary tract cancer. *Cancer.* 2006;106:1339–46.
  45. Zeng ZC, Tang ZY, Fan J, et al. Consideration of the role of radiotherapy for unresectable intrahepatic cholangiocarcinoma: a retrospective analysis of 75 patients. *Cancer J.* 2006;12:113–22.
  46. Fiorentini G, Aliberti C, Turrisi G, et al. Intraarterial hepatic chemoembolization of liver metastases from colorectal cancer adopting irinotecan-eluting beads: results of a phase II clinical study. *In Vivo.* 2007;21:1085–91.
  47. Aliberti C, Benea G, Tilli M, Fiorentini G. Chemoembolization (TACE) of unresectable intrahepatic cholangiocarcinoma with slow-release doxorubicin-eluting beads: preliminary results. *Cardiovasc Intervent Radiol.* 2008;31:883–8.
  48. Fiorentini G, Rossi S, Bonechi F, et al. Intra-arterial hepatic chemoembolization in liver metastases from neuroendocrine tumors: a phase II study. *J Chemother.* 2004;16:293–7.
  49. Malagari K, Pomoni M, Kelekis A, et al. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma. *Cardiovasc Intervent Radiol.* 2010;33(3):541–51.
  50. Cantore M, Mambrini A, Fiorentini G, et al. Phase II study of hepatic intraarterial epirubicin and cisplatin, with systemic 5-fluorouracil in patients with unresectable biliary tract tumors. *Cancer.* 2005;103:1402–7.
  51. Mambrini A, Del FA, Pacetti P, et al. Intra-arterial and systemic chemotherapy plus external hyperthermia in unresectable biliary cancer. *Clin Oncol (R Coll Radiol).* 2007;19:805–6.
  52. Melichar B, Cerman J Jr, Dvorak J, et al. Regional chemotherapy in biliary tract cancers—a single institution experience. *Hepato-gastroenterology.* 2002;49:900–6.
  53. Mambrini A, Guglielmi A, Pacetti P, et al. Capecitabine plus hepatic intra-arterial epirubicin and cisplatin in unresectable biliary cancer: a phase II study. *Anticancer Res.* 2007;27:3009–13.
  54. Feisthammel J, Schoppmeyer K, Mossner J, et al. Irinotecan with 5-FU/FA in advanced biliary tract adenocarcinomas: a multicenter phase II trial. *Am J Clin Oncol.* 2007;30:319–24.
  55. Lee MA, Woo IS, Kang JH, Hong YS, Lee KS. Epirubicin, cisplatin, and protracted infusion of 5-FU (ECF) in advanced intrahepatic cholangiocarcinoma. *J Cancer Res Clin Oncol.* 2004;130:346–50.
  56. Nehls O, Oettle H, Hartmann JT, et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: a prospective multicentre phase II trial. *Br J Cancer.* 2008;98:309–15.
  57. Sasaki T, Isayama H, Nakai Y, et al. Multicenter, phase II study of gemcitabine and S-1 combination chemotherapy in patients with advanced biliary tract cancer. *Cancer Chemother Pharmacol.* 2010;65(6):1101–7.
  58. Takezako Y, Okusaka T, Ueno H, et al. Phase II study of cisplatin, epirubicin and continuous infusion of 5-fluorouracil in patients with advanced intrahepatic cholangiocellular carcinoma (ICC). *Hepato-gastroenterology.* 2008;55:1380–4.