Phase 2 Trial of Concurrent Bevacizumab and Transhepatic Arterial Chemoembolization in Patients With Unresectable Hepatocellular Carcinoma

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BACKGROUND: Vascular endothelial growth factor is up-regulated in hepatocellular carcinoma (HCC) and is further up-regulated after transhepatic arterial chemoembolization. The authors of this report conducted a phase 2 trial to evaluate the safety and efficacy of bevacizumab combined with chemoembolization in patients with unresectable HCC. METHODS: Patients who had an Eastern Cooperative Oncology Group performance status of 0 to 2, a Child-Pugh score of A or B, and Barcelona Clinic Liver Cancer stage B or C HCC were eligible. Treatment consisted of bevacizumab every 2 weeks and chemoembolization during the third week of a 6-week cycle for up to 3 cycles over 6 months. The primary endpoints were safety and efficacy. RESULTS: Twenty-five patients received chemoembolization and bevacizumab. The most common grade 3 and 4 events after the first treatment cycle were leukopenia (12%), fatigue (12%), and hyponatremia (12%). Serious toxicities that had a known association with bevacizumab were observed in 4 patients. Thirty-day mortality was 0%. The median time to tumor progression for the targeted lesions was not reached, and overall survival was 10.8 months. The objective response rate was 60% using enhancement response evaluation criteria, and the disease control rate was 100%. CONCLUSIONS: Concurrent treatment with bevacizumab and chemoembolization was safe in carefully selected patients and demonstrated antitumor activity in patients with unresectable HCC. These results support the further development of bevacizumab combined with chemoembolization as a treatment for unresectable HCC. Cancer 2013;119:1042-9. © 2012 American Cancer Society.

KEYWORDS: transhepatic arterial chemoembolization, hepatocellular carcinoma, bevacizumab.

INTRODUCTION
Hepatocellular carcinoma (HCC) constitutes a major health issue, accounting for more than 598,000 deaths annually worldwide.1,2 The majority of patients with HCC presents with advanced-stage disease, and the median survival is <6 months.3 Recently, phase 3 clinical trials demonstrated that sorafenib prolongs the survival of patients with advanced HCC.4,5 However, in those trials, the median survival still was <1 year. For many patients who have unresectable, intermediate stage HCC, transhepatic arterial chemoembolization often is recommended as the preferred treatment option.6,7 Several studies have demonstrated the survival benefit of chemoembolization.8 However, 1 of the main limitations of chemoembolization is the high incidence of recurrence. Even among patients who have an initial response to such treatment, the 3-year cumulative recurrence rate can be as high as 65%.9

One possible reason for recurrence after chemoembolization is the stimulation of angiogenesis by chemoembolization-induced tumor hypoxia.10 HCC is a highly vascular tumor in which angiogenesis mediated by vascular endothelial growth factor (VEGF) contributes to growth and metastatic spread. It has been demonstrated that VEGF overexpression is a prognostic indicator of poor survival in patients with HCC.11–14 VEGF is further up-regulated immediately after chemoembolization, and VEGF levels after treatment are an independent predictor of tumor response and survival.15–17

Bevacizumab, a humanized monoclonal antibody, prevents binding of VEGF to its receptors, thereby inhibiting VEGF-mediated angiogenesis. Bevacizumab normalizes tumor vasculature, thereby improving tumor uptake of concomitantly administered therapeutic agents.18 In addition, it has been demonstrated that bevacizumab modulates blood vessels and drug response in HCC in vitro.19 Recently, our group described our experience combining sorafenib with chemoembolization and demonstrated that this approach was safe and potentially efficacious.20 However, there is a paucity of data on the use of chemoembolization combined with other biologic agents like bevacizumab.

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We postulated that combined treatment with chemoembolization and bevacizumab may potentiate cytotoxic effects on HCC by preventing chemoembolization-induced up-regulation of angiogenesis. In turn, combined chemoembolization and bevacizumab therapy may facilitate tumor uptake of the cytotoxic agents delivered through chemoembolization. To examine these hypotheses, we conducted a prospective, 2-center, single-arm phase 2 trial to evaluate the safety and efficacy of bevacizumab combined with chemoembolization in patients with unresectable HCC.

MATERIALS AND METHODS

Study Population and Eligibility Criteria

Patients aged ≥ 18 years with a diagnosis of unresectable HCC based on either histology obtained by needle biopsy or a hypervascular lesion > 2 cm on cross-sectional imaging and an α-fetoprotein level of ≥ 200 ng/mL were evaluated for this study. Eligibility and exclusion criteria were similar to those used in other phase 2 trials reported by our group. This study was approved by our institutional review boards and was conducted in accordance with the principles of the Declaration of Helsinki. The trial was registered at clinicaltrials.gov (identifier NCT00335829).

Study Design

Patients received intravenous bevacizumab (10 mg/kg; Genentech, South San Francisco, Calif) and chemoembolization for up to 3 cycles over 6 months (Fig. 1A). Five of the first 6 patients, however, had not fully recovered from chemoembolization in the third week and required withholding of the second dose of bevacizumab in week 3. After this, the protocol was amended (Fig. 1B). Patients received bevacizumab and chemoembolization on the same day (but not exactly at the same time). After completion of the last treatment cycle, follow-up included clinic visits and cross-sectional imaging every 8 to 12 weeks. After completion of the protocol, patients were allowed to receive other therapies. Chemoembolization procedures were performed as previously described.

Safety and Efficacy

Each study visit included a clinical assessment, laboratory evaluations, and toxicity assessments (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0). In the event of a dose-limiting toxicity (DLT), bevacizumab was withheld until resolution; no dose reductions were allowed. The interim safety assessment demonstrated no DLTs; therefore, enrollment was continued per protocol.

Tumor response was assessed using contrast-enhanced magnetic resonance imaging at baseline, 3 weeks after each chemoembolization, and 4 weeks after completion of the final treatment cycle. Images were viewed centrally by an independent diagnostic radiologist who did not know that the patients were part of a clinical trial. Responses were evaluated and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Specifically, tumor response was assessed by standard criteria (Response Evaluation Criteria in Solid Tumors [RECIST]) and by assessing tumor enhancement. In the tumor enhancement assessment, a CR was defined as 100% tumor necrosis of the target lesion(s) upon completion of any of 3 cycles of chemoembolization therapy, a PR was defined as > 50% tumor necrosis of the target lesion(s) upon completion of any of 3 cycles of chemoembolization therapy, SD was indicated if patients did not meet criteria for CR or PR and did not demonstrate evidence of disease progression. SD was measured from the start of treatment until the criteria for progression were met, taking as reference the smallest measurements of target lesion(s) recorded since treatment started. PD was defined as either the reappearance or increased tumor enhancement > 25% in the target lesion(s). Response was assessed considering the entire volume of the tumor(s) by an experienced radiologist (I.R.K.).
Statistical Considerations
Our primary endpoint was the time to tumor progression (TTP) of the targeted lesions. Our analysis followed the current recommendations for the design of HCC clinical trials, which recommend censoring deaths during follow-up in patients without evidence of radiologic progression. Secondary endpoints included the TTP of nontargeted lesions within the liver and the overall TTP. TTP time points were measured from the initiation of therapy until documentation of progression. Overall survival (OS) was measured both from the date of diagnosis of unresectable HCC and from the time of initiation of therapy until death.

Survival endpoints were estimated using the Kaplan-Meier method. The objective response rate (ORR) (defined as the total of CRs and PRs of targeted lesions) and the disease control rate (defined as the total of CRs, PRs, and stable responses of targeted lesions) were compared using linear regression models fit with generalized estimating equations to account for multiple tumors in the same patient. All analyses were conducted using statistical freeware (R version 2.11.1; R Foundation for Statistical Computing, Vienna, Austria; www.rproject.org).

RESULTS
Patient Characteristics
Between September 2006 and April 2009, in total, 26 patients consented to participate in the study and were enrolled. One patient left the study before receiving chemoembolization and after receiving 1 administration of bevacizumab. This patient was included in the safety analysis but was excluded from the efficacy analysis. The characteristics of the study population are listed in Table 1.

Safety and Treatment Toxicity
Overall, the 26 enrolled patients received a total of 43 cycles of therapy. The median number of treatment cycles per patient was 2 (range, 1–3 treatment cycles per patient). At the last follow-up, 6 patients were alive and were censored at that time. The median number of chemoembolization treatments per patient was 2 (range, 1–3 chemoembolization treatments). The median number of weeks of bevacizumab therapy delivered per patient was 4 weeks (range, 1–9 weeks). In total, 14 bevacizumab administrations were withheld because of adverse events (n = 6, before protocol amendment).

During cycle 1, 100% of patients experienced some toxicity. The most common toxicities during weeks 1 and 2 of cycle 1 (ie, bevacizumab only) included hyperbilirubinemia (12%), elevated prothrombin (8%), nausea (8%), and elevated aspartate aminotransferase (8%). In general, most toxicities during weeks 1 and 2 of cycle 1 were not severe (grade 1 and 2, 83%; grade 3 and 4, 17%) (Table 2). Uncommon grade 3 and 4 toxicities that were observed in weeks 1 and 2 of cycle 1 were fatigue (4%), ascites (4%), hemorrhage of esophageal varices (4%), hypokalemia (4%), and encephalopathy (4%). After week 3 of cycle 1 (ie, chemoembolization administration), each

| Table 1. Baseline Patient Characteristics (N = 26) |
|-----------------------------------------------|
| Characteristic                                | No. of Patientsa |
| Institution                                   |                  |
| Northwestern University                        | 10               |
| Johns Hopkins University                      | 16               |
| Age: Mean [range], y                          | 64 [31–85]       |
| Sex                                           |                  |
| Men                                           | 21               |
| Women                                         | 5                |
| Race                                          |                  |
| Asian                                         | 2                |
| African American                              | 5                |
| Caucasian                                     | 18               |
| Hispanic                                      | 1                |
| ECOG performance status                       |                  |
| 0                                             | 17               |
| 1                                             | 8                |
| 2                                             | 1                |
| Etiology                                      |                  |
| HBV                                           | 4                |
| HCV                                           | 12               |
| Other                                         | 10               |
| Previous treatment                            |                  |
| None                                          | 15               |
| Transhepatic arterial chemoembolization        | 4                |
| Radioembolization                             | 3                |
| Systemic chemotherapy                         | 1                |
| Resection                                     | 4                |
| Transplantation                               | 1                |
| Cirrhosis                                     |                  |
| Yes                                           | 20               |
| No                                            | 6                |
| Portal vein thrombosis                        |                  |
| Yes                                           | 5                |
| No                                            | 21               |
| Child-Pugh score                              |                  |
| A                                             | 20               |
| B                                             | 6                |
| C                                             | 0                |
| BCLC stage                                    |                  |
| B                                             | 9                |
| C                                             | 17               |
| AFP > 200 ng/mL                               |                  |
| No. of patients                               | 8                |
| Mean/Median AFP, ng/mL                        | 14,323/3373      |
| Metastatic disease                            |                  |
| Yes                                           | 6                |
| No                                            | 20               |

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus.

*All data are expressed as the number of patients unless stated otherwise.
| Toxicities                  | Grade 1–2 | Grade 3–4 | Grade 1–2 | Grade 3–4 | Grade 1–2 | Grade 3–4 | Grade 5 |
|-----------------------------|-----------|-----------|-----------|-----------|-----------|-----------|--------|
| Blood/bone marrow           | 0         | 0         | 22        | 5         | 20        | 2         | 0      |
| Anemia                      | —         | —         | 9         | 1         | —         | —         | —      |
| Leukocytopenia              | —         | —         | 4         | 3         | 7         | —         | —      |
| Lymphopenia                 | —         | —         | 7         | 1         | 10        | 2         | —      |
| Cardiovascular              | 0         | 0         | 4         | 3         | 3         | 1         | 0      |
| Heart failure               | —         | —         | —         | 1         | —         | —         | —      |
| Edema                       | —         | —         | 2         | 1         | 1         | 1         | —      |
| Ischemia                    | —         | —         | —         | 1         | —         | —         | —      |
| Coagulation                 | 3         | 0         | 10        | 0         | 5         | 0         | 0      |
| Constitutional              | 2         | 1         | 19        | 5         | 14        | 1         | 0      |
| Fatigue                     | 1         | 1         | 9         | 3         | 10        | 2         | —      |
| Night sweats                | —         | —         | 1         | 1         | —         | —         | —      |
| Weight loss                 | 1         | —         | 5         | 1         | 2         | —         | —      |
| Dermatologic                | 0         | 0         | 0         | 0         | 3         | 0         | 0      |
| Endocrine                   | 0         | 0         | 0         | 0         | 2         | 0         | 0      |
| Gastrointestinal            | 5         | 1         | 28        | 4         | 12        | 1         | 1      |
| Ascites                     | —         | 1         | —         | 1         | 2         | 1         | —      |
| Anorexia                    | 1         | —         | 10        | 1         | 2         | —         | —      |
| Duodenal perforation        | —         | —         | —         | —         | —         | —         | —      |
| Nausea                      | 2         | —         | 3         | 1         | 1         | —         | —      |
| Vomiting                    | 1         | —         | 5         | 1         | 2         | —         | —      |
| HEENT                       | 0         | 0         | 2         | 0         | 0         | 0         | 0      |
| Hemorrhage/bleeding         | 0         | 1         | 2         | 0         | 3         | 0         | 0      |
| Esophageal varices          | —         | 1         | —         | —         | —         | —         | —      |
| Hepatic function            | 7         | 0         | 32        | 5         | 24        | 2         | 0      |
| Elevated ALT                | 1         | —         | 6         | 1         | 2         | —         | —      |
| Elevated AST                | 2         | —         | 6         | 1         | 5         | 1         | —      |
| Hyperbilirubinemia          | 3         | —         | 4         | 2         | 3         | 1         | —      |
| Liver failure               | —         | —         | 1         | —         | —         | —         | —      |
| Infection                   | 0         | 0         | 2         | 2         | 1         | 1         | 0      |
| Cellulitis                  | —         | —         | 1         | —         | —         | —         | —      |
| Clostridium difficile       | —         | —         | —         | —         | —         | —         | —      |
| Colangitis                  | —         | —         | —         | —         | —         | —         | —      |
| Metabolic                   | 3         | 1         | 18        | 8         | 21        | 2         | 0      |
| Hyperglycemia               | —         | —         | 6         | 2         | 10        | 1         | —      |
| Hypocalcemia                | —         | —         | 2         | 1         | 1         | 1         | —      |
| Hypokalemia                 | —         | —         | 2         | 2         | 1         | —         | —      |
| Hyponatremia                | 1         | 1         | 4         | 3         | 4         | —         | —      |
| Musculoskeletal             | 0         | 0         | 0         | 0         | 0         | 1         | 0      |
| Fracture                    | —         | —         | —         | —         | —         | —         | —      |
| Neurologic                  | 2         | 1         | 7         | 2         | 5         | 2         | 0      |
| Cord compression            | —         | —         | —         | —         | —         | —         | —      |
| Delirium                    | —         | —         | —         | 1         | —         | —         | —      |
| Encephalopathy              | —         | 1         | —         | —         | —         | —         | —      |
| Psychosis                   | —         | —         | —         | 1         | —         | —         | —      |
| Stroke                      | —         | —         | —         | —         | —         | —         | —      |
| Pain                        | 1         | 0         | 9         | 6         | 7         | 0         | 0      |
| Abdominal, NOS              | —         | —         | 5         | 1         | —         | —         | —      |
| Epigastric                  | —         | —         | —         | 1         | —         | —         | —      |
| RUQ                         | 1         | —         | 3         | —         | 4         | —         | —      |
| Chest                       | —         | —         | —         | 2         | —         | —         | —      |
| Other                       | —         | —         | 1         | 2         | 3         | —         | —      |
| Pulmonary                   | 1         | 0         | 1         | 1         | 1         | 0         | 0      |
| Dyspnea                     | —         | —         | 1         | 1         | 1         | —         | —      |
| Renal                       | 1         | 0         | 2         | 2         | 2         | 0         | 0      |
| Acute renal failure         | —         | —         | —         | 1         | —         | —         | —      |
| Proteinuria                 | 1         | —         | 1         | 1         | 2         | —         | —      |
| Respiratory                 | 1         | 0         | 3         | 0         | 5         | 0         | 0      |
| Total                       | 25        | 5         | 161       | 43        | 128       | 14        | 1      |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HEENT, head/eyes/ear/nose/throat; NOS, not otherwise specified; RUQ, right upper quadrant; TACE, transarterial chemoembolization.
patient experienced at least 1 toxicity. The most common grade 1 and 2 toxicities after chemoembolization consisted of hypoalbuminemia (44%), anorexia (40%), anemia (36%), fatigue (36%), lymphopenia (28%), elevated alanine aminotransferase (24%), elevated aspartate aminotransferase (24%), and hyperglycemia (24%). One patient had a grade 1 vascular event, which consisted of an arterial dissection involving the hepatic artery. The dissection was noted on a magnetic resonance image before chemoembolization and was noted again incidentally during the chemoembolization procedure, but it did not preclude successful completion of the procedure. This event and other lower grade events resolved without any sequelae. The most common grade 3 and 4 toxicities after chemoembolization were leukocytopenia (12%), fatigue (12%), and hyponatremia (12%).

In total, during cycle 1, 25 of 25 patients experienced at least 1 toxicity associated with bevacizumab plus chemoembolization. However, the overall toxicity profile for cycle 1 was good, because only 21% of all reported toxicities were grade 3 or 4, and most reported toxicities were grade 1 or 2 (79%). Possible bevacizumab-related toxicities included 1 patient who had chest pain 1 week after the third bevacizumab dose during cycle 1.

Fourteen patients received 2 or 3 cycles of therapy. In general, the incidence of grade 1 and 2 toxicities after 2 or 3 cycles was greater than the toxicity after cycle 1 alone and included hypoalbuminemia (79%), lymphopenia (71%), fatigue (71%), hyperglycemia (71%), and leukocytopenia (50%). Similar to the first cycle, 1 patient had a grade 1 vascular event, which consisted of an arterial dissection involving the hepatic artery during the second cycle that resolved without sequelae. Also, like the first cycle, most toxicities during cycles 2 and 3 were not severe (grade 1 and 2, 90%; grade 3 and 4, 10%). The most common grade 3 and 4 toxicity after 2 or 3 cycles was lymphopenia (14%); other grade 3 and 4 adverse events included edema, fatigue, ascites, elevated aspartate aminotransferase, hyperbilirubinemia, hyperglycemia, hypocalcemia, cord compression, and fracture, all of which occurred in only 1 patient each (7%). Possible bevacizumab-related toxicities included 1 patient who was admitted for *Clostridium difficile* infection after completing cycle 2. During this admission, the patient suffered from volume overload, and a more detailed cardiac workup revealed atrial flutter and cardiomyopathy. A second patient, who had cerebral vascular disease diagnosed on follow-up imaging, experienced a cerebral infarct during cycle 2. A separate patient suffered a grade 5 toxicity because of a ruptured duodenal ulcer. This patient had completed the second cycle of therapy and was diagnosed with a duodenal perforation, developed sepsis, and subsequently died (Table 2).

### Efficacy

Twenty-three patients were evaluable for tumor response on imaging studies. One patient withdrew from the study before follow-up imaging, a second patient left the study because of cardiac toxicity, and a third patient was lost to follow-up. Treatment was associated with a decrease in median tumor size from 5.8 cm to 4.6 cm (*P* < .0001); in addition, the median tumor enhancement decreased from 100% to 25% (*P* < .0001) (Table 3). The ORR was 35% according to RECIST and 60% according to tumor enhancement (Table 3). According to either tumor response criteria, the disease control rate was 100% while the patients underwent treatment. One patient had an objective response that lasted >2 years and, consequently, was successfully bridged to transplantation. It is noteworthy that, on pathologic analysis of the explanted liver, there was no evidence of residual viable HCC.

Among the targeted lesions, the majority had no evidence of progression at 6 months (86%) or at 1 year (53%). The median TTP of the targeted lesion from the start of therapy was not reached at last follow-up. In contrast, the median TTP in nontargeted lesions was 9.1 months (95% confidence interval [CI], 6.5–9.1 months).

| TABLE 3. Efficacy, n = 23 Patients |
|-----------------------------------|
| Efficacy Variable, n = 36 Lesions  | Value                  |
| Tumor size                        |                        |
| Baseline: Median/range, cm        | 5.8/1.4–20             |
| Post-therapy: Median/range, cm    | 4.6/1.4–16.2           |
| Mean percentage change from baseline [95% CI], % | –9.9 [–15 to 4.8]     |
| *P* < .0001                       |                        |
| Contrast-enhancement              |                        |
| Baseline: Median/range, %         | 100/50–100             |
| Post-therapy: Median/range, %     | 25/0–100               |
| Mean percentage change from baseline [95% CI], % | –57 [–71 to 43]      |
| *P* < .0001                       |                        |
| Response of the targeted lesion: No. of Patients (%) |            |
| Tumor enhancement                 |                        |
| CR                                | 4 (17)                 |
| PR                                | 10 (43)                |
| SD                                | 9 (39)                 |
| PD                                | 0 (0)                  |
| RECIST                            |                        |
| CR                                | 0 (0)                  |
| PR                                | 8 (35)                 |
| SD                                | 15 (65)                |
| PD                                | 0 (0)                  |

Abbreviations: CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
The median overall TTP from the initiation of therapy was 7.2 months (95% CI, 5.8–9.1 months), and the corresponding 6-month and 1-year progression-free survival rates were 65% (95% CI, 47%–90%) and 23% (95% CI, 9%–60%), respectively. Responders tended to have a longer TTP (7.5 months) than patients who had SD (5.8 months; \( P = .09 \)) (Fig. 2A).

The median OS was 10.8 months (95% CI, 4.8–24.7 months) from the start of therapy and 23.6 months (95% CI, 12.8–31.5 months) from diagnosis. Responders tended to have a longer median OS (21.7 months) than patients who only had SD (4.8 months; \( P = .09 \)) (Fig. 2B).

**DISCUSSION**

There has been increasing interest in combining systemic agents with intra-arterial therapy for patients with advanced HCC. Although it has been demonstrated that intra-arterial therapy effectively induces necrosis of targeted lesions, there is concern that liver-directed therapy may induce hypoxia-mediated factors that could stimulate neoangiogenesis and new tumor growth.\(^{10,15–17}\) Our group has had an interest in intra-arterial therapy for HCC as well as combination therapy using intra-arterial therapy with systemic agents.\(^ {20} \) The current report is important, because we demonstrate that the combination of chemoembolization and bevacizumab is safe in carefully selected patients. It has been demonstrated that chemoembolization causes systemic side effects, largely related to the postembolization syndrome, which typically include nausea, vomiting, abdominal pain, fever, and loss of appetite.\(^ {22} \) The toxicities we report here with combined chemoembolization and bevacizumab therapy were expected and were mostly related to chemoembolization, because the toxicity profile of combination therapy was similar to that reported after chemoembolization alone.\(^ {22} \) In addition to defining the safety and toxicity profile of combined chemoembolization and bevacizumab therapy, we noted that this combination had considerable antitumor effects when received by patients with unresectable HCC. Specifically, we noted no radiologic progression of targeted lesions during therapy. Collectively, these data suggest that combined therapy with chemoembolization and bevacizumab is safe and may have efficacy in treating patients with advanced HCC.

To date, the use of combined chemoembolization and bevacizumab in the advanced HCC population has not been reported previously in detail. In 1 unpublished pilot study, patients with HCC who underwent chemoembolization subsequently were randomized to receive either concurrent, continuous bevacizumab or observation.\(^ {26} \) The reported preliminary results in 7 patients indicated that the combination of chemoembolization and bevacizumab was relatively well tolerated. However, grade 3 and 4 toxicities were reported in 4 patients and included hypertension and a variceal bleed. A separate, randomized, placebo-controlled trial of chemoembolization and bevacizumab in patients with advanced HCC recently was reported.\(^ {27} \) In that trial, patients received standard chemoembolization and either placebo or bevacizumab (5 mg/kg) every 2 weeks over 48 weeks. However, the trial was stopped early because of safety concerns related to bevacizumab toxicity. In the current study, we noted an overall toxicity profile for combined therapy with
chemoembolization and bevacizumab. Specifically, although 100% of patients experienced some toxicity during cycle 1, the overwhelming toxicities were grade 1 or 2 (79%). The lower toxicity reported during cycle 1 of chemoembolization and bevacizumab in our study most likely was multifactorial. We closely monitored blood pressure both before and during therapy; in addition, all patients who had large varices on imaging were required to undergo endoscopy and banding before therapy. Our study design also allowed for bevacizumab treatment breaks of several weeks between cycles, which may help explain the better toxicity profile. It is important to note, however, that toxicity with chemoembolization and bevacizumab did appear to increase with additional cycles of therapy. In fact, 7 of 14 patients (50%) who received 2 or 3 cycles of therapy experienced grade 3 and 4 toxicity. Perhaps more important, several of these events appeared to be related to bevacizumab and were similar to those reported in other phase 1/2 studies with bevacizumab.28,29 Thus, although combined chemoembolization and bevacizumab appears to be safe, judicious patient screening and selection are needed. More investigation will be required to define better whether more than 1 cycle of combined chemoembolization and bevacizumab is indeed more toxic.

Combined chemoembolization and bevacizumab therapy did demonstrate antitumor effects. While patients were on the protocol, combination therapy yielded a 100% disease control rate as assessed by radiographic criteria. Perhaps as expected, no evaluable patient had a CR according to RECIST. These findings are consistent with data from other studies that evaluated chemoembolization or antiangiogenic agents, which noted that tumors that respond to these types of treatments do not necessarily “shrink” or have a decrease in their greatest cross-sectional dimension.30,31 Rather, tumor necrosis—instead of tumor size—appears to be a better indicator of therapeutic efficacy.24 In the current study, we noted clear evidence of tumor necrosis of the lesions that were targeted by chemoembolization. There was a significant decrease in contrast enhancement of the targeted lesions after treatment with combined chemoembolization and bevacizumab. On the basis of these criteria, we noted an ORR of 60% after combined chemoembolization and bevacizumab in our study most likely was multifactorial. We closely monitored blood pressure both before and during therapy; in addition, all patients who had large varices on imaging were required to undergo endoscopy and banding before therapy. Our study design also allowed for bevacizumab treatment breaks of several weeks between cycles, which may help explain the better toxicity profile. It is important to note, however, that toxicity with chemoembolization and bevacizumab did appear to increase with additional cycles of therapy. In fact, 7 of 14 patients (50%) who received 2 or 3 cycles of therapy experienced grade 3 and 4 toxicity. Perhaps more important, several of these events appeared to be related to bevacizumab and were similar to those reported in other phase 1/2 studies with bevacizumab.28,29 Thus, although combined chemoembolization and bevacizumab appears to be safe, judicious patient screening and selection are needed. More investigation will be required to define better whether more than 1 cycle of combined chemoembolization and bevacizumab is indeed more toxic.

In conclusion, the results from this single-arm, phase 2 study provide important data that begin to define the safety and efficacy of combined locoregional and systemic treatment of patients with advanced HCC. We noted that combined chemoembolization and bevacizumab was safe in carefully selected patients and had antitumor activity. These results support further development and investigation of chemoembolization combined with bevacizumab as a treatment for advanced, unresectable HCC.

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