Single-center Comparison of Three Chemoembolization Regimens for Hepatocellular Carcinoma

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ABSTRACT

Purpose: Transarterial chemoembolization regimens for hepatocellular carcinoma (HCC) vary, without a gold-standard method. The present study was performed to evaluate outcomes in patients with HCC treated with doxorubicin/ethiodized oil (DE), cisplatin/doxorubicin/mitomycin-c/ethiodized oil (CDM), or doxorubicin drug-eluting beads (DEBs).

Materials and Methods: Patients received the same regimen at all visits, without crossover. Groups were compared based on Child–Pugh disease status, tumor/node/metastasis stage, and Barcelona Clinic Liver Cancer stage. Imaging outcomes were assessed based on modified Response Evaluation Criteria in Solid Tumors to calculate tumor response (ie, sum of complete and partial response), progressive disease (PD), and time to progression (TTP).

Results: A total of 228 infusions were performed in 122 patients: 59 with DE, 30 with CDM, and 33 with DEBs. The groups had similar Child–Pugh status ($P = .45$), tumor/node/metastasis stages ($P = .5$), and Barcelona Clinic Liver Cancer scores ($P = .22$). Follow-up duration was similar among groups ($P = .24$). Patients treated with DE underwent significantly more treatments (2.3 ± 1.4) than those treated with CDM (1.6 ± 0.7; $P = .004$) or DEBs (1.4 ± 0.6; $P < .0001$). Compared with DE (51%), tumor response was significantly more common with CDM (84%; $P = .003$) or DEBs (82%; $P = .004$). PD was significantly more likely with DE (37%) than with CDM (13%; $P = .02$) or DEBs (9%; $P = .004$). TTP was similar between groups ($P = .07$). CDM and DEBs were similar in regard to disease progression ($P = .6$) and response ($P = .83$).

Conclusions: During a similar follow-up period, patients treated with CDM or DEB chemoembolization showed a significantly higher response rate and a lower incidence of tumor progression, with fewer required treatment sessions, than those treated with DE chemoembolization.

ABBREVIATIONS

CDM = cisplatin/doxorubicin/mitomycin-c/ethiodized oil, CR = complete response, DE = doxorubicin/ethiodized oil, DEB = drug-eluting bead, HCC = hepatocellular carcinoma, mRECIST = modified Response Evaluation Criteria in Solid Tumors, PACS = picture archiving and communication system, PD = progressive disease, PR = partial response, TTP = time to progression

Transarterial chemoembolization is an effective palliative treatment for hepatocellular carcinoma (HCC) (1,2) and is currently used as a first-line treatment option in patients who have unresectable multinodular HCC without portal vein thrombosis and with preserved liver function (3,4). Patients with this presentation often overlap with individuals being considered for liver transplantation based on Milan or University of California, San Francisco, criteria.

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Therefore, chemoembolization is also frequently used as an adjuvant therapy to keep tumors from progressing beyond transplantation criteria or to attempt to downstage HCC in patients with tumors that do not meet the Milan criteria for transplantation (5–8).

Despite the reported successful outcomes with this procedure, data comparing the relative efficacy of various chemotherapeutic regimens are still limited, and no standardized treatment protocol currently exists (9,10). Two commonly referenced prospective randomized trials (1,2) used different drugs: single-agent doxorubicin and cisplatin, respectively. Other commonly reported protocols for HCC describe the use of doxorubicin alone with ethiodized oil (1,11) or in combination with cisplatin and mitomycin-c (12–14). The development and increased use of drug-eluting beads (DEBs) has created an additional variable to consider in treatment planning (15,16).

In all patients with HCC, disease control is crucial because tumor response based on contrast enhancement correlates with increased survival (17–19). Additionally, disease progression portends decreased survival in patients being treated for palliative reasons, and can also result in elimination from consideration for listing on the transplantation list, or removal from the list (7,18,20,21). Our group has used three treatment protocols to treat HCC: doxorubicin/ethiodized oil (DE), cisplatin/doxorubicin/mitomycin-c/ethiodized oil (CDM), and DEBs. The purpose of the present study is to compare the relative efficacy of these three treatment protocols as measured by tumor response, tumor progression, and time to progression (TTP) of tumors in patients treated for HCC.

MATERIALS AND METHODS

This study was approved by our institutional review board and was compliant with the Health Insurance Portability and Accountability Act of 1996. All patients undergoing chemoembolization between January 2001 and July 2011 were reviewed by using our radiology information system. From this search, we found 252 patients who underwent chemoembolization for primary HCC at our institution. Patients were referred by hepatology or medical oncology staff and reviewed in multidisciplinary conferences before treatment. Patients who had been treated with a single consistent regimen with reviewable imaging on our picture archiving and communication system (PACS) were included in the study. Fifty-two patients were excluded for crossing over to a different treatment regimen. An additional 77 patients were excluded for not having pre- or postprocedural imaging available on our PACS, which was installed in 1999 and modified in 2006, allowing outside images to be imported. Until 2006, only the dictated reports from outside studies were available, so patients with only this information available were censored based on concern for inconsistency in read quality. This left 122 patients available for evaluation. The treatment method was determined by operator preference and was consistent among each treating interventional radiologist throughout the trial. DE was the standard regimen for two operators throughout the study and was the only method used at our institution until 2007. A third interventional radiologist who joined the group used a CDM regimen upon arriving in 2007. There was a transition to the use of DEBs in 2009 when ethiodized oil became unavailable, followed by powdered cisplatin becoming unavailable. Patient data for these procedures were retrospectively reviewed and included in the study cohort.

Chemoembolization

The procedures described here were performed in keeping with Society of Interventional Radiology quality improvement guidelines (22). In all cases, arterial subselection and embolization were performed as distally as possible by using a microcatheter based on tumor size and location by four fellowship-trained interventional radiologists with 4–17 years of experience. Planning for complete treatment in a given arterial territory was consistent for all three groups. No more than one lobe of the liver was treated per session. Embolization with each regimen was performed until arterial stasis was achieved in the supplying segmental or subsegmental arteries (22,23). Details of each treatment regimen are as follows.

DE Group. Doxorubicin (50–100 mg) was mixed in 2–10 mL of ethiodized oil, based on tumor diameter, and infused under fluoroscopic guidance. This was followed by embolization of the tumor-feeding arteries with absorbable gelatin sponge slurry (Surgifoam; Ethicon, Somerville, New Jersey).

CDM Group. Fifty milligrams of cisplatin, 50 mg of doxorubicin, and 10 mg of mitomycin-c were mixed in 3–10 mL of ethiodized oil, based on tumor diameter, and infused into the selected arterial supply under fluoroscopic guidance. The tumor-feeding arteries were then embolized with Surgifoam slurry.

DEB Group. Doxorubicin (100 mg) was adsorbed on two vials of DEBs (LC Bead; Biocompatibles, Farnham, United Kingdom). For tumors smaller than 6 cm in diameter, 100–300 -μm beads were used. For larger tumors, one vial of 100–300 -μm DEBs and one vial of 300–500 -μm DEBs were used.

Response Determination

Follow-up contrast-enhanced magnetic resonance (MR) or computed tomography (CT) imaging was obtained 4–5 weeks after treatment of the entire cancer-bearing liver. MR was performed on a 1.5- or 3-T magnet, and included axial T1-weighted precontrast and dynamic postcontrast images, T2-weighted images, and subtraction images. Three-phase CT was performed by using helical acquisition on a multidetector scanner. MR imaging was used unless patients could not suspend respiration adequately to allow diagnostic quality