Conventional versus Drug-Eluting Bead Transarterial Chemoembolization for Neuroendocrine Tumor Liver Metastases

Mina S. Makary, MD, Jordan Kapke, BS, Vedat Yildiz, MS, Xueliang Pan, PhD, and Joshua D. Dowell, MD, PhD

ABSTRACT

Purpose: To compare outcomes of conventional transarterial chemoembolization with drug-eluting bead (DEB) chemoembolization for treatment of neuroendocrine tumor liver metastases.

Materials and Methods: This single-center, retrospective study evaluated 177 transarterial chemoembolization treatments (78 conventional chemoembolization treatments using ethiodized oil–based cisplatin, mitomycin C, and doxorubicin and 99 DEB chemoembolization treatments using doxorubicin-loaded 100–300 μm DEBs) from 2012 to 2015. Hepatic disease distribution was 93% bilobar for both groups with largest lesion size 5.0 cm ± 2.7. No difference was noted in regard to lesion size or distribution, carcinoid syndrome, or pancreastatin production. Clinical outcomes including complications; liver function tests (LFTs); and radiologic (modified Response Evaluation Criteria in Solid Tumors), biochemical (pancreastatin levels), and symptomatic responses were evaluated at 1-month follow-up.

Results: Higher symptomatic response (complete and partial) was identified with conventional transarterial chemoembolization compared with DEB chemoembolization (47% vs 30%; $P < .05$). Patients receiving DEB transarterial chemoembolization experienced lower elevation of LFTs (aspartate aminotransferase, 39 U/L vs 122 U/L; alanine aminotransferase, 20 U/L vs 93 U/L; bilirubin, 0.001 mg/dL vs 0.123 mg/dL; $P < .05$) and less postembolization syndrome (50% vs 67%; $P < .05$). Patients undergoing first-time DEB transarterial chemoembolization had lower periprocedural octreotide maximum rate requirements (58 μg/h vs 66 μg/h; $P < .05$). No difference was observed in biochemical ($P = .60$) or radiologic ($P < .20$) responses.

Conclusions: Conventional transarterial chemoembolization yields better symptomatic response and may be preferred for patients experiencing carcinoid symptoms. DEB transarterial chemoembolization, with lower LFT elevations and postembolization syndrome incidence, may be preferred for patients with poor liver function.

ABBREVIATIONS

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DEB = drug-eluting bead, LFT = liver function test, NET = neuroendocrine tumors

Neuroendocrine tumors (NETs) are rare malignancies that are diagnosed in 2.5–5.3 patients per 100,000 people annually with increasing incidence in the United States (1). First described in 1890, this heterogeneous group of neoplasms is primarily derived from the gastrointestinal tract and pancreas and is characterized by the capacity to synthesize hormonally active products (2). Although these tumors are typically indolent and do not manifest symptoms for years, approximately 46%–93% of patients with NETs present with metastatic disease, particularly to the liver (3,4). The liver is the most common site of distant metastatic disease, and its involvement is the most important prognostic factor for patient quality of life and survival (5).

From the Division of Vascular and Interventional Radiology (M.S.M., J.D.D.), Department of Radiology, The Ohio State University Wexner Medical Center, 395 West 12th Avenue, Columbus, OH 43210; and College of Medicine (J.K.) and Center for Biostatistics (V.Y., X.P.), The Ohio State University, Columbus, Ohio. Received January 15, 2016; final revision received May 10, 2016; accepted May 12, 2016. **Address correspondence to** J.D.D.; E-mail: Joshua.Dowell@OSUMC.edu

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Despite the widespread use of transarterial chemoembolization, the exact role of transarterial chemoembolization in NET hepatic lesions is not well established and is still being elucidated (6). Owing to the rarity of NETs and heterogeneity of the disease itself, large prospective randomized controlled trials have been lacking (7). Although DEB transarterial chemoembolization has an undeniable favorable drug-release profile, antitumoral advantages, and decreased systemic side effects, a large phase II randomized clinical trial in patients with hepatocellular carcinoma failed to demonstrate improved response or survival benefits compared with conventional transarterial chemoembolization (8). Furthermore, data regarding liver-specific toxicity, clinical outcomes, radiologic response, or intraprocedural tolerance of DEB transarterial chemoembolization versus conventional transarterial chemoembolization for NETs are sparse (9). The primary aim of this study is to investigate the clinical outcomes of conventional transarterial chemoembolization compared with DEB chemoembolization for treatment of metastatic NETs to the liver—specifically the perioperative outcomes; symptomatic, clinical, and morphologic responses; and survival for both transarterial chemoembolization approaches.

MATERIALS AND METHODS

Study Design and Patient Populations

This retrospective cohort study was approved by the institutional review board and was performed with waiver of informed consent. From June 2012 to June 2015, 105 consecutive patients with histologically confirmed NET liver metastases underwent transarterial chemoembolization therapy at a single tertiary care academic institution performed by 6 interventional radiologists. Of the 49 patients receiving conventional transarterial chemoembolization and 56 patients receiving DEB chemoembolization, 42 patients in each group were undergoing a first-time transarterial chemoembolization treatment. Reviewing the data from both cohorts, 78 conventional transarterial chemoembolization treatments were compared with 99 DEB transarterial chemoembolization treatments. As a result of a universal shortage of cisplatin used in conventional transarterial chemoembolization, an institutional change was implemented in January 2014 to switch to DEB transarterial chemoembolization for all patients with NETs. Therefore, patients treated from June 2012 to January 2014 were treated with triple-drug conventional transarterial chemoembolization (doxorubicin, mitomycin C, and cisplatin), and patients treated from January 2014 to June 2015 were treated with doxorubicin-loaded DEB transarterial chemoembolization. Patient demographics for both transarterial chemoembolization groups are shown in Table 1. No difference was noted in regard to lesion size or distribution, carcinoid syndrome, or pancreastatin production.

Assessment before transarterial chemoembolization included evaluation of liver involvement with computed tomography or magnetic resonance imaging performed within 1 month of treatment, liver function tests (LFTs; alanine aminotransferase, aspartate aminotransferase, and bilirubin), carcinoid tumor markers (pancreastatin), and pathologic confirmation (Table 1). Histologic data were available for 72 (92%) patients receiving conventional transarterial chemoembolization and 84 (85%) patients receiving DEB chemoembolization. Tumor aggressiveness was characterized based on the histologic mitotic index measurement, per the 2010 World Health Organization NET grading guidelines (10). The classification is divided into grade 1 with < 2 mitoses per 10 high-power fields and a Ki-67 $\leq 2\%$, grade 2 with 2–20 mitoses and a Ki-67 of 3%–20%, and grade 3 with > 20 mitoses and a Ki-67 $> 20\%$. Grades 1, 2, and 3 were formerly called carcinoid, well-differentiated, and poorly differentiated tumors (10).

Chemoembolization Methods

All patients undergoing transarterial chemoembolization were maintained on a continuous intravenous octreotide infusion (2 μg/mL) on the day of the procedure, with the rate adjusted as needed to control carcinoid symptoms and/or vital signs, especially during the transarterial chemoembolization session. Prophylactic broad-spectrum antibiotics, allopurinol, and hydrocortisone were also routinely given before the procedure. The procedure was performed under moderate sedation. A lobar or segmental approach of the target hepatic artery was performed, and the chemotherapeutic treatment was delivered. For patients receiving conventional transarterial chemoembolization, the injection was an emulsion of doxorubicin (30 mg), cisplatin (50 mg), mitomycin C (20 mg), and ethiodized oil 37% (10 mL) and delivered in a ratio of 1:1 with iohexol contrast agent. For patients receiving DEB transarterial chemoembolization, 2 vials of 100–300 μm DEBs (LC Beads; BTG International Ltd, London, United Kingdom) loaded with 100 mg of doxorubicin were used and administered until stasis. If persistent antegrade flow was encountered after either conventional transarterial chemoembolization or DEB drug delivery, embolization was continued until stasis occurred using 300–500 μm bland particles. Stasis was defined as the absence of antegrade flow within a vessel, such that even slow administration of contrast material results in reflux for 5 cardiac beats after injection. After the procedure, patients were admitted to the hospital and monitored overnight with expected discharge the next day.

Treatment Response

Imaging evaluation was performed within 3 months $\pm$ 7 days of transarterial chemoembolization using the same imaging modality that was used for imaging before treatment, either triple-phase computed tomography or contrast-