BRIEF REPORT

Doxorubicin-Eluting Intra-arterial Therapy for Pediatric Extra-Abdominal Desmoid Fibromatoses: A Promising Approach for a Perplexing Disease

Eldad Elnekave, MD, Eli Atar, MD, Shirah Amar, MD, Elchanan Bruckheimer, MBBS, Michael Knizhnik, MD, Isaac Yaniv, MD, Tal Dujovny, MD, Meora Feinmesser, MD, and Shifra Ash, MD

ABSTRACT

Systemic doxorubicin is effective for desmoid fibromatosis (DF), but its use is limited by dose-dependent cardiotoxicity. A protocol of selective intra-arterial doxorubicin drug-eluting embolization (DEE) was designed to maximize target tissue efficacy of doxorubicin, while minimizing systemic exposure. Four children with recurrent or refractory DF were treated between 2014 and 2017. Tumor volumes were reduced by 54%–97% over a follow-up interval of 6–32 months. A single patient experienced transient lower extremity paresthesia (Common Terminology Criteria for Adverse Events grade I). Further investigation is needed to better establish these promising results for doxorubicin DEE in DF treatment.

ABBREVIATIONS

DEE = drug-eluting embolization, DF = desmoid fibromatosis

Desmoid fibromatoses (DFs) are rare and clinically elusive: nearly a quarter of asymptomatic tumors regress spontaneously, and the remainder progress along a variable course of growth and invasion into adjacent neurovascular structures and viscera. Surgery has been the cornerstone of DF treatment, although recurrence after surgery is reported in 20% to > 50% of resections for DF (1). Recurrent tumors tend to behave more invasively than the initial disease (2), often necessitating more aggressive and potentially morbid interventions. Contemporary DF management reflects a trend away from primary resection (3,4).

Nonsurgical options remain suboptimal. Radiotherapy has shown benefit when combined with resection (5), although its use must be balanced by the potential for complications and secondary malignancies, particularly in children. Isolated limb perfusion has shown promising results for locally advanced disease, although it too must be weighed against the potential for vascular toxicity. Early reports of cryoablation have been encouraging, but this treatment is as yet limited to small, extra-abdominal tumors. Systemic treatments range broadly from nonsteroidal anti-inflammatory drugs and hormonal therapy to targeted tyrosine kinase inhibitors and cytotoxic chemotherapy (6). Overall, systemic treatment is associated with at least partial response in a minority (8%–36%) of patients (7,8).

Multicenter retrospective reviews have shown that DF treatment regimens including doxorubicin are associated with better outcomes (9,10). The largest prospective study of doxorubicin for DFs reported a partial or complete response in all patients, leading the authors to conclude that the combination of doxorubicin plus dacarbazine should be considered for first-line chemotherapy in symptomatic DFs (11). However, the efficacy of doxorubicin is accompanied by its dose-dependent risk of cardiotoxicity (12), which is of particular concern in the pediatric setting (13). To maximize doxorubicin efficacy locally

From the Departments of Diagnostic Radiology (E.E., E.A., M.K.) and Pathology (M.F.) and Institute of Oncology (E.E.), Davidoff Center, Rabin Medical Center, Beilinson Hospital, Petach Tikva 4941492, Israel; The Rina Zaizov Hematology-Oncology Division (S.Am., I.Y., S.As.) and Section of Pediatric Cardiology (E.B.), Schneider Children's Medical Center of Israel, Petach Tikva, Israel; Pediatric Oncology Unit (T.D.), Emek Medical Center, Afula, Israel; and Sackler Faculty of Medicine (E.E., E.A., S.Am., E.B., I.Y., M.F., S.As.), Tel Aviv University, Tel Aviv, Israel. Received December 12, 2017; final revision received and accepted April 5, 2018. **Address correspondence to** E.E.; E-mail: Eldad.elnekave@gmail.com; Twitter handle: @E_Elnekave_MD

None of the authors have identified a conflict of interest.

J Vasc Interv Radiol 2018; ■:1–7

https://doi.org/10.1016/j.jvir.2018.04.009

while minimizing systemic toxicity, a protocol of selective intra-arterial doxorubicin drug-eluting embolization (DEE) was designed for extra-abdominal DF treatment. The present feasibility study reports the first 4 patients treated under this protocol.

MATERIALS AND METHODS

Patients

All patients had biopsy-proven DFs, were discussed in multidisciplinary tumor board, and were treated between January 2014 and July 2017 (Table 1). Institutional review board approval was obtained, and informed consent was provided before all interventions. During this interval, 8 patients with DFs were seen, including 3 with intra-abdominal DFs and 5 with extra-abdominal DFs. One Gardner syndrome patient with a scalp DF was not treated with doxorubicin DEB transarterial chemoembolization because diagnostic angiography failed to identify feeding arteries. The remaining 4 patients are described.

Patient 1 was referred at 4 years of age with a right axillary 15.4 × 14.1 × 14.4 cm DF (Fig 1a–d). The tumor compressed the right hemithorax and brachial plexus, causing almost complete paralysis of her arm and hand. An R1 surgical excision had been performed 2 years earlier. Subsequent treatment with vincristine, actinomycin, cyclophosphamide, ifosfamide, carboplatin, and etoposide failed to control the disease. Magnetic resonance (MR) imaging showed no change following a 3-month course of dacarbazine and doxorubicin. After failing a subsequent 12-month trial of weekly vinblastine (5 mg/m^2) and methotrexate (30 mg/m^2), patient 1 underwent the first of 3 selective doxorubicin DEB transarterial chemoembolization treatments.

Patient 2 was referred at 16 years of age with a 10.9 × 10.8 × 4.6 cm protuberant, tender right gluteal mass (Fig 2a–d). The first of 2 doxorubicin DEB transarterial chemoembolization treatments were initiated after a trial of weekly vinblastine (5 mg/m^2) and methotrexate (30 mg/m^2) failed to control the disease.

Patient 3 was referred at 15 years of age with a 5-month history of increasing fullness in his right shoulder and decreasing neck mobility. MR imaging performed at presentation demonstrated a 12.2 × 7.1 × 5.4 cm mass extending from the right supraclavicular fossa to the sternocleidomastoid muscle and brachial plexus (Fig 3a, b). Treatment with 26 cycles of weekly vinblastine (5 mg/m^2) and methotrexate (30 mg/m^2) over 6 months failed to control the disease. At this point, the patient was referred for the first of 3 doxorubicin DEB transarterial chemoembolization treatments.

Patient 4 presented at 13 years of age with a rubbery right T8-T9 intercostal mass (Fig 4a–d). Her past medical history was significant for a partial deletion of chromosome 10 (q23/31-q24.2) with congenital defects, including aortic and pulmonary artery dilatation, scoliosis, and a developmental delay. By age 11 years, she had idiopathic bone marrow failure; bone marrow biopsy revealed moderately hypoplastic marrow with dysplastic changes in the megakaryocytic lineage. Following an R1 resection, surgical pathology confirmed DF. Local recurrence was noted within 6 months; by 13 months, the recurrence was larger and more infiltrative than the initial DF. Bone marrow failure precluded systemic therapy, and the patient was referred for selective doxorubicin DEB transarterial chemoembolization.

Treatment and Follow-up

All patients were treated by 1 of 2 fellowship-trained interventional radiologists with 7 and 20 years of experience (E.E. and E.A.). Superselective arterial catheterization was achieved from the right common femoral artery using 4-F or 5-F guiding catheters and a 2.4-F coaxial microcatheter. Tumor vessels were identified based on anatomic origin, morphologic features (hypertrophy, abnormal tortuosity), and flow into the angiographic blush in the DF. One vial containing 2 mL of 75–150 μm DC Beads (Biocompatibles UK Ltd, Farnham, United Kingdom) was loaded with 25–50 mg doxorubicin per treatment. Each vial was then diluted to 10 mL using 4 mL 0.9% normal saline and 4 mL Omnipaque 320 (GE Healthcare, Little Chalfont, United Kingdom) iodinated contrast material.

The embolization endpoint was delivery of the doxorubicin dose using the minimal amount of embolic material—a "pruned tree" appearance of the vascular territory was commonly observed, although stasis of flow was not observed. Each patient underwent 1–3 treatments, spaced 4 months apart (Table 2). Between 1 and 6 feeding arteries were treated per patient, with embolization of no more than 2 vessels per session. Consolidation of blood flow toward the tumor and away from nontarget tissue was achieved using standard angiographic techniques, such as microcoil embolization of small arteries (intercostal, internal mammary) and temporary balloon occlusion of large ones (brachial) distal to the tumor. Intraprocedural cone-beam computed tomography was used as needed to confirm tumor coverage and exclude nontarget opacification. All patients were admitted for observation overnight, and all were discharged the following morning.

MR imaging was performed between 2 and 3 months after each treatment and at 6-month intervals following completion of treatment. MR imaging was used for all imaging before the procedure and follow-up imaging and consisted of axial and coronal T2, T2 fat-saturated or short tau inversion recovery, and dual phase T1 sequences. Characteristic features of DFs include heterogeneously hyperintense T2 (or short tau inversion recovery) signal among interspersed hypointense bands (14). Histologically, the ratio of T2 signal to hypointense bands correlates to the degree of cellularity versus fibrotic matrix within DFs (15). Decreased tumor volume and loss of T2 intensity are reliable markers of DF responses to systemic treatment (16,17) and served as primary imaging response metrics. Tumor volume was assessed by manual segmentation on T1-weighted imaging (IntelliSpace Portal; Philips Healthcare, Best, Netherlands) by a diagnostic radiologist with 12 years of experience.