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Case Report

Transarterial chemoembolization as a part of multi-modality treatment with drug-eluting beads for locally advanced breast cancer: A case report ☆,☆☆

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ABSTRACT

Locally advanced breast cancer (LABC) is generally treated with combined-modality therapy including systemic chemotherapy, surgery, radiotherapy, and targeted therapy due to its nature of rapid onset of metastatic disease and poor prognosis. In this case report, we present a 61-year-old female who suffered from a huge protruding breast mass (16.2cm) with superficial ulcerative wound noted for three months. LABC was diagnosed via core needle biopsy and PET-CT examination. Initially, she received combined systemic chemotherapy, hormone therapy and radiation therapy; however, severe necrosis caused rupture in part of the breast mass and extensive wound discharge resulting in difficulty in wound care and prolonged disease course. Trans-arterial chemoembolization with drug-eluting beads (DEB-TACE) was applied as a part of combined-modality therapy for shortening the time before surgery. HepaSphere (as one of the DEB) loaded with high dose of epirubicin (total 80mg) was infused intra-arterially due to the nature of slow-releasing effect and longer duration of ischemic effect. Shortly after DEB-TACE following in about 40 days, surgery was smoothly performed. Post-operative adjuvant target therapy and adjuvant chemotherapy with taxane were administered. There was no evidence of local recurrence or distal metastases after 9 months of follow-up. It is suggested that performing DEB-TACE prior to surgery becomes a part of multimodality treatment of LABC to achieve better local control, better wound care and shortened treatment course.

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Introduction

Breast cancer is the most common malignancy affecting women globally and is the leading cause of cancer death in this population. Locally advanced breast cancer (LABC) is defined as T3 (>5cm), T4 (invasion to chest wall and/or skin) primary tumor or N2 (fixed axillary), N3 (internal mammary) lymph node metastasis without distant metastasis by National Comprehensive Cancer Network guidelines [1]. Generally, a combined-modality therapy including chemotherapy, operation, radiation with or without target therapy is applied, but the overall prognosis is still poor [2-3]. Good local control and down-staging of the disease can increase the possibility of surgery; however, systemic chemotherapy might not be administered or is aborted because of treatment failure, intolerance to side effects, multiple comorbidities and patient's refusal. The availability of alternative treatments for locoregional control is desirable. Transarterial chemoembolization with drug-eluting beads (DEB-TACE) has been widely used in treating hepatic malignancy [4,5]. Its efficacy and safety have been well-established. DEB-TACE has also been applied in pulmonary, mediastinal and hepatic metastases from breast cancer [6,7].

To our knowledge, there has been no previous report using DEB-TACE as a part of combined therapy with systemic chemotherapy, radiation and target therapy for a primary breast malignancy; consequently, a case of LABC treated additionally by DEB-TACE is reported herein.

Case report

A 61-year-old female was admitted to the hospital with a left breast huge protruding mass and reddish skin discoloration noted for at least three months (Fig. 1). Superficial ulcerative wound (5 × 6cm) over breast mass with much light-yellowish discharge was noted on physical examination. Laboratory tests revealed elevated white count ($11.5 \times 10^3/\mu\text{L}$) [normal range: $4-10 \times 10^3/\mu\text{L}$], C-reactive protein concentration (10.2 mg/dL) [normal ≤ 3 mg/dL], CA-153 (154.5 U/ml) [normal ≤ 31 U/ml] and decreased Hb (9.7 g/dL) [normal range: 14-18 g/dL]. PET-CT showed suspicious primary left breast cancer (16.2cm) with chest wall & skin involvement, metastatic lymphadenopathy at the left axillary (levels I, II, III) and left internal mammary regions (Fig. 2). Pathology diagnosis (Fig. 3) via core needle biopsy revealed histological grade 3 invasive ductal carcinoma with hormone studies negative of ER,PR, equivocal staining of HER2 and 45% of Ki-67 index. The clinical cancer stage was T4cN3bM0 Stage IIIC (Union for International Cancer Control guidelines). The patient then received one course of systemic chemotherapy (epirubicin $90\text{mg}/\text{m}^2$ and cyclophosphamide $600\text{mg}/\text{m}^2$), concomitant target regimen with Herceptin (trastuzumab) $8\text{mg}/\text{m}^2$ and Perjeta (pertuzumab) 840mg in the loading dose as well as radiation therapy of 50Gy. About one month later, necrotic and broken bulky part of breast mass was removed painlessly by the surgeon (Fig. 4), with the problem of poor wound care due to extensive wound discharge being noted. Trans-arterial



Fig. 1 – Photo of initial presentation. Left breast huge protruding mass and reddish skin discoloration.

chemoembolization with drug-eluting beads (DEB-TACE) was suggested for better locoregional tumor control by the interventional radiologic department in the medical team meeting. Informed consent for the DEB-TACE was obtained after discussion with the patient and her family. Under local anesthesia, the right femoral artery was punctured, then a 5-French sheath was inserted into the patient's right femoral artery. Left subclavian digital subtraction angiography was done via a 4-French catheter (Headhunter type; Terumo, Tokyo, Japan) and strong enhancement and engorged vessels in the tumor site and multiple axillary lymph nodes were revealed. Selective arteriography displayed tumor feeders including left internal mammary, lateral thoracic and subscapular arteries, and they were selectively catheterized via a 3-French microcatheter (Progreat, Terumo). Each artery was embolized with DEB including two vials of HepaSphere particles 30-60 μm and 50-100 μm in size; each vial loaded with 40mg of Epirubicin and 10cc of contrast medium) with very slow injection rate (1 ml/min). The endpoint of intra-arterial embolization was a significant sluggish blood flow near stasis (clearing of contrast column within 2-5 heartbeats). Only local heat, slight heaviness, and soreness on her left breast were complained about during the procedure. Several episodes of fever up to 38.9 degrees centigrade were sustained for three days along with soreness and pain over left upper arm as well as weakness of raising arm during this time. The above symptoms were improved after prescription of steroid, NSAID, and local ice-packing. Poor wound condition occurred two days later with sometimes more or less amount of stinky odor discharge, and prophylactic antibiotics were given with changing of wound dressing more often. This condition showed much improvement after three weeks. The white cell count decreased to 2200/ μL within two weeks then gradually increased to normal level. Tumor marker CA-153 from 154.5 U/mL decreased to 31.3 U/mL in five weeks of follow-up. Pre-operative CT

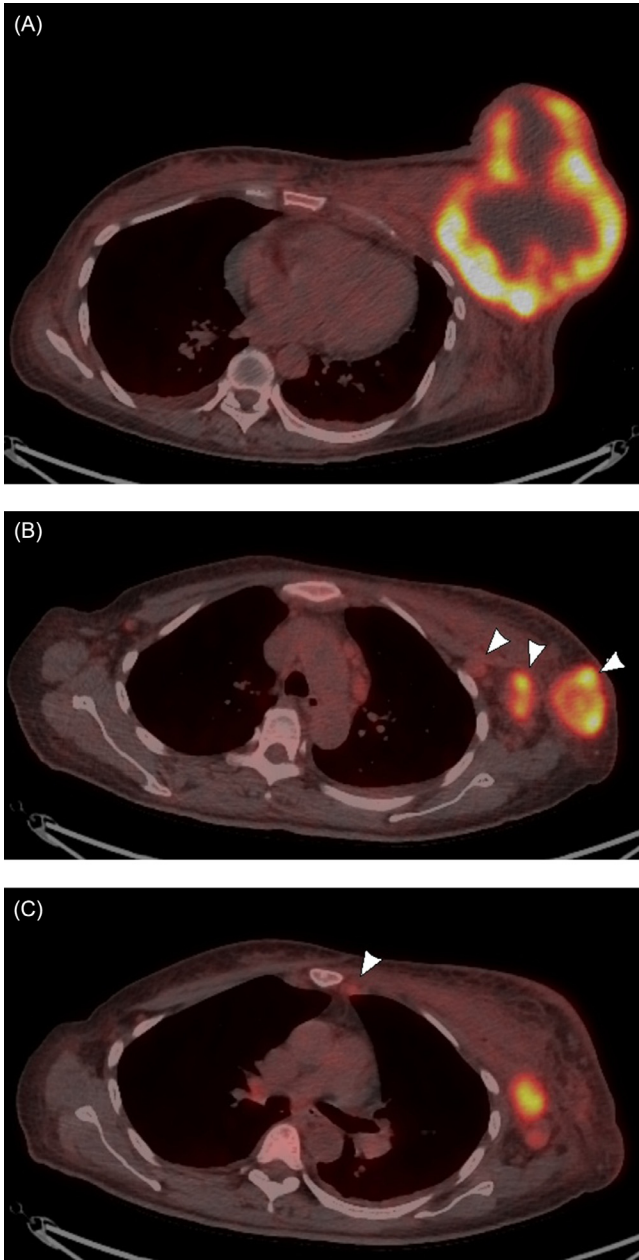


Fig. 2 – PET-CT axial images showing (A) increased FDG avidity of left breast mass (16.2cm) with chest wall & skin involvement and metastatic lymphadenopathy at the left axilla (B) and internal mammary region (C).

(Fig. 5) was performed 40 days after DEB-TACE (i.e., four months after initial systemic chemotherapy) revealing partial shrinkage of volcanic crater-like left breast tumor (9cm) with invading skin & chest wall, central necrotic left axillary level I LAP (largest 4.7cm) as well as remission of levels II-III LAP. A 43.8% reduction in largest tumor diameter and less skin erythema surrounding tumor were noted after the multimodality treatment. Under general anesthesia, left modified radical mastectomy (i.e., left total mastectomy and axillary lymph nodes dissection) and the fascio-cutaneous flap harvested from abdominal wall to cover the left chest wall skin defect

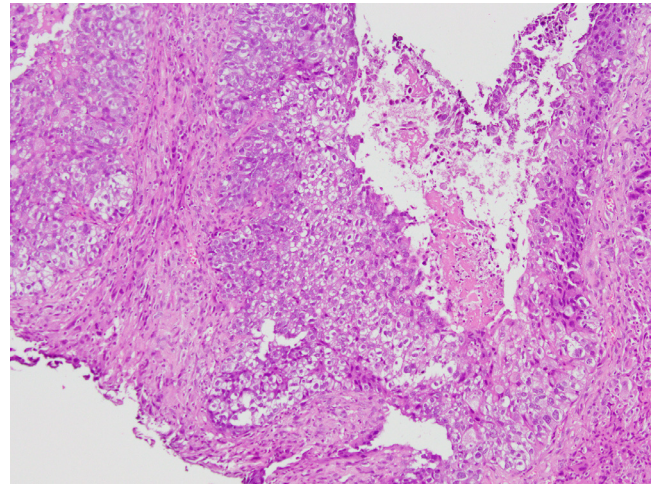


Fig. 3 – Pathology via core needle biopsy. Hematoxylin and eosin stained section of core needle biopsy demonstrating sheets of pleomorphic neoplastic cells with prominent nucleoli and some necrosis.



Fig. 4 – Photo after initial combined-modality therapy. Broken breast mass visible with a large cross-section wound.

were smoothly carried out. Surgical specimen was evaluated and pathology (Fig. 6) showed grade III (Nottingham histologic score) invasive ductal carcinoma with 10cm in greatest dimension of invasive component, extensive degree of tumor necrosis, skin and nipple involvement with ulceration, and two axillary lymph node metastases (largest 4.7cm in diameter). Post-operative adjuvant dual target therapy with trastuzumab and pertuzumab and adjuvant chemotherapy with taxane were then administered at OPD for a one-year course. There was no evidence of local recurrence or distal metastases after 9 months of follow-up.

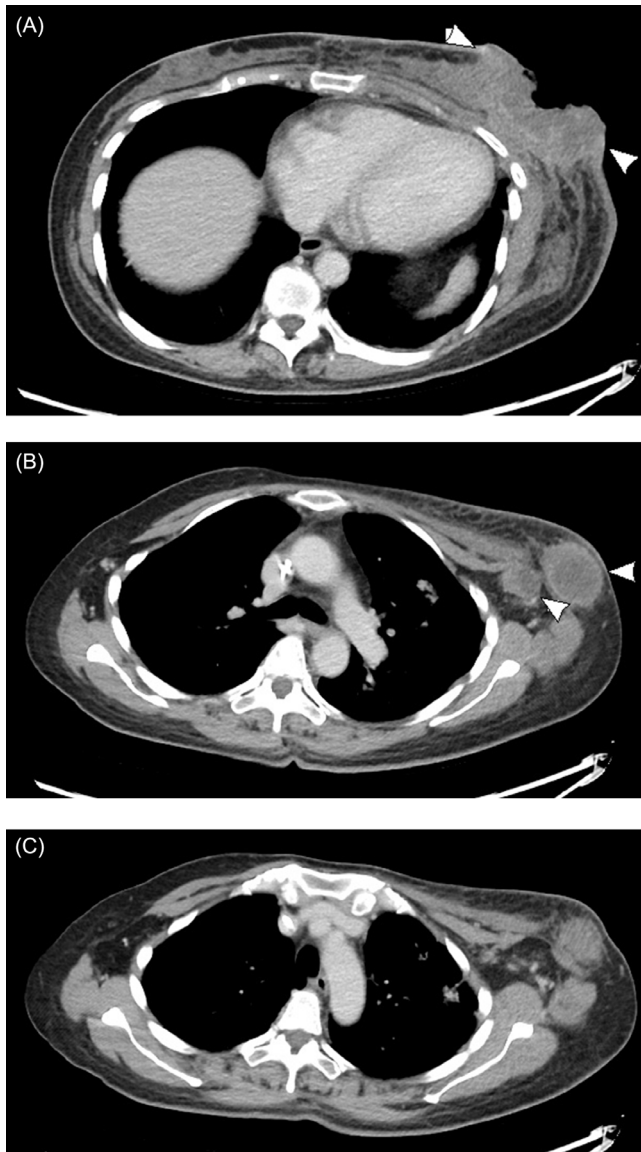


Fig. 5 – Pre-operative CT axial enhancing images after DEB-TACE and other combined-modality therapy. (A) Partial shrinkage of volcanic-crater like left breast tumor (9cm) with invading skin & chest wall. (B) Central necrotic change of left axillary level I LAP (largest 4.7cm) as well as (C) remission of levels II-III LAP.

Discussion

Breast cancer is the most common cancer diagnosed for females [8]. Despite being confined to the breast and regional lymph nodes, LABC often displays the rapid onset of metastatic disease, causing high mortality rates. Traditionally, preoperative systemic (i.e., neoadjuvant) chemotherapy has been used for downstaging to make an inoperable tumor operable. Du et al [9] compared the efficacy of intra-arterial infusion chemotherapy (IAIC) with that of intra-venous route as neoadjuvant chemotherapy in breast cancer patients.

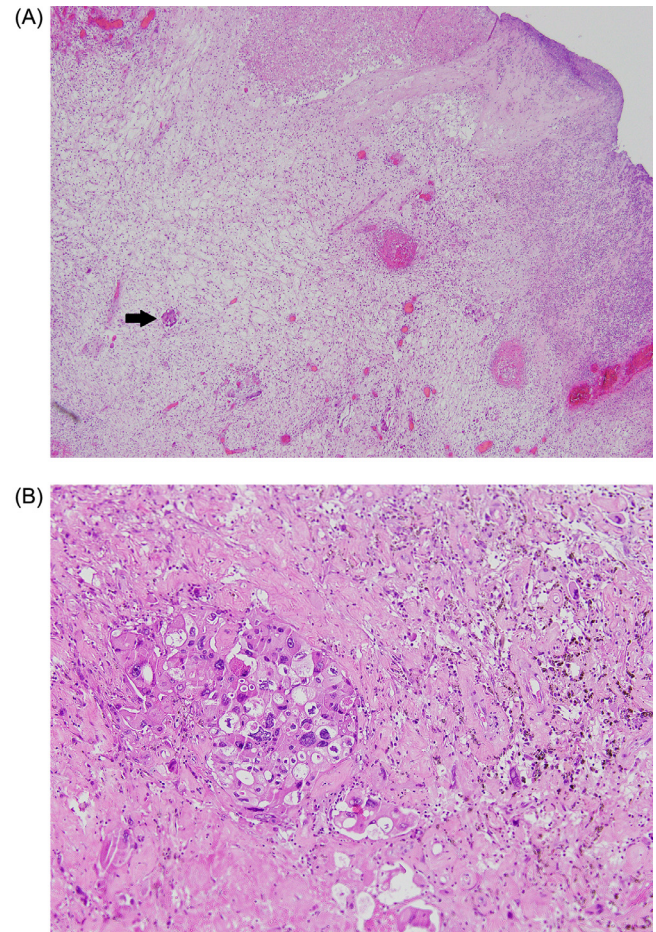


Fig. 6 – Pathology via total mastectomy. Hematoxylin and eosin stained section (A) demonstrating skin ulcer (left upper) and tumor emboli (arrow). Section (B) demonstrating hyalinizing stroma and residual tumor nests. The tumor cells show more pleomorphism

Combined multiple therapeutic drugs with CEF or MEF protocol (includes cyclophosphamide, epirubicin, 5-fluorouracil, mitomycin C) were used both in intraarterial and intravenous groups, while intra-arterial embolization was done with 1000-1400 μm gelatin sponge after intra-arterial chemo-infusion. The remission rate in the intra-arterial group (93.18%) was significantly higher than in the intra-venous group (62.5%); besides, the mean time interval between chemotherapy and surgery in the intra-arterial group was obviously shorter than that in the intra-venous group (25 days vs 56 days; $P < .05$). Arterial infusion with embolization may serve as an effective alternative strategy in the neoadjuvant chemotherapy for breast cancer.

For patients with LABC, any single local modality, radiotherapy or surgery, is not suggested because of high incidence of distal failure and worse prognosis. Murakmai et al. [10] used IAIC combined with radiotherapy with or without surgery for patients with locally advanced or recurrent breast cancer. Intra-arterial chemotherapy without embolization was performed as the initial treatment with anticancer drugs consisting of doxorubicin, cisplatin, and mitomycin C in most cases.

The clinical objective and complete response rates achieved were 78% and 9% respectively after IAIC treatment. In that study, 73% of patients had evident viable cancer before radiotherapy (67% of patients post operation and 88.9% of inoperable patients), with local recurrence occurring in 6%, and the 5-year local control rates were 89%. The results clearly indicate that radiotherapy was able to control remnant disease.

Drug-eluting beads (DEBs) loaded with chemotherapy have been developed in treating primary and metastatic hepatic malignancy. Previous studies [4,11] reported that systemic concentrations of chemotherapeutic drug were significantly lower in patients treated with DEB-TACE than in conventional TACE using lipiodol, chemotherapeutic drugs & gelfoam pledgets.

DEBs can be slowly released after TACE, and prolong the duration of ischemic effect while intensifying the drug delivery to the tumor. Their capacity to reduce the amount of chemotherapy reaching the systemic circulation achieves a better tolerance for patients with a low rate of adverse reactions [12]. HepaSphere, as one of the DEBs, consists of superabsorbent polymer microspheres with negatively charged character. The attraction between positive and negative charges can load positively charged anticancer agents such as anthracyclines (epirubicin, doxorubicin, etc.), irinotecan, and docetaxel.

Kennoki et al [13] first adopted HepaSphere as a treatment choice for LABC. Intraarterial infusion of multiple anticancer drugs was carried out prior to embolization with docetaxel- or Adriamycin- loaded HepaSphere. The patient received surgery after three sessions of DEB-TACE and had been followed for 1 year without signs of recurrence. Wang et al [14] used similar DEB (CalliSphere) for the treatment of unresectable LABC. In the study, 40–80 mg of epirubicin was loaded without arterial infusion of other chemotherapy drugs concomitantly. All 15 patients received surgery successfully and the response rate was 73% 5 months after operation. DEB-TACE offers short-term efficacy for the clinical treatment of LABC and can be a new treatment option for inoperable patients.

In the present case, we initiated multimodality treatment including systemic chemotherapy, radiotherapy, and target therapy due to the bulky nature of her LABC. Then, the huge tumor underwent necrosis and broke up with a large cross-section wound, which caused difficulty in wound care. For shortening the time before surgery, one session of DEB-TACE was carried out. Two vials of HepaSphere (total 50mg) loaded with high dose of epirubicin (total 80mg) was infused due to the nature of slowly releasing DEB and large area of hypervascular tumor zones in left breast and axilla. Intraarterial infusion of multiple anticancer drugs was not performed, which might increase the procedure time; besides, DEB-TACE with single anticancer drug achieved good effect for treating LABC in a previous study [14]. Shortly following DEB-TACE about 40 days later, surgery was smoothly done.

Conclusion

Combined multimodality treatment including radiotherapy and target therapy may be effective initially, but might cause

severe necrotic wound, so the treatment course before surgery would become prolonged. In conclusion, DEB-TACE is safe and highly effective in shrinking the bulky LABC, improving wound care after combined multimodality treatment, and shortening the hospitalization period. We suggest performing DEB-TACE prior to surgery as a part of the multimodality treatment including radiotherapy and target therapy. To demonstrate the efficacy of this therapeutic option, further studies with larger sample sizes will be required.

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