Locoregional Therapy for Liver Metastases From Breast Cancer

Current intra-arterial treatment options for women with hepatic-dominant breast cancer metastases.

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The American Cancer Society estimated that 252,710 women were diagnosed with invasive breast cancer and 40,610 women succumbed to breast cancer in 2017.[1] This means that 1 in 8 women will be diagnosed with breast cancer in their lifetime.[2] Once women develop advanced disease, more than half develop hepatic metastases,[3,4] and of those women, nearly 20% progress to fulminant hepatic failure and die.[4,5] For patients with metastatic disease, the current National Comprehensive Cancer Network guidelines recommend treatment based on the site of disease, whether the patient is pre- or postmenopausal, and the hormonal status of the primary tumor (estrogen receptor/progesterone receptor, human epidermal growth factor receptor 2/neu). However, if a patient fails three sequential rounds of chemotherapy, the guidelines recommend novel therapies offered in clinical trials versus supportive care.[6] Surgical resection and percutaneous ablation techniques can be considered for patients with limited disease. Unfortunately, most patients present with tumor burden that is not amendable to these potentially curative therapies.

Interventional oncologists have increasingly employed transcatheter intra-arterial therapies for patients with primary and secondary hepatic malignancies. These treatments aim to slow hepatic disease progression, while mitigating the systemic side effects resulting from cytotoxic chemotherapies. This article reviews the current intra-arterial treatment options for women with hepatic-dominant breast cancer metastases.

TREATMENT MODALITY SELECTION

Transcatheter intra-arterial embolotherapies can be classified as macroembolic (eg, transarterial embolization, conventional transarterial chemoembolization [cTACE], and drug-eluting embolic [DEE]-TACE) or microembolic (eg, transarterial radioembolization [TARE]). Macroembolic therapies promote tumor ischemia/hypoxia when combined with chemotherapy (cTACE and DEE-TACE), whereas microembolic therapies deliver a radioisotope for radiotherapy.

Conventional Transarterial Chemoembolization

This form of chemoembolization utilizes an aqueous drug emulsified with Lipiodol (poppy seed oil) (Guerbet LLC). This emulsion is delivered to the tumor(s) of interest followed by embolization agents, which aims to prevent drug washout. Only small retrospective studies have been performed on the use of cTACE for treating liver-dominant breast cancer metastases (Table 1).[7-9] Of the 241 patients included in these studies, 56% to 70% of patients developed mild postembolization syndrome, which manifests as abdominal pain, nausea, and vomiting. There was a 40% to 64% rate of response on follow-up imaging, and median overall survival ranged from 10.2 to 32.5 months. However, cTACE was combined with ablation in one of these studies, and if this study is not included and only cTACE survival rates are considered, median overall survival is 10.2 to 12 months.

Drug-Eluting Embolic Transarterial Chemoembolization

DEE-TACE employs small microspheres (40–500 µm) loaded with a chemotherapeutic agent (typically doxorubicin or irinotecan). The microspheres serve as an embolic agent, and they also elute the payload drug at its site of deposition. In the literature, only two retrospective

TABLE 1. SUMMARY OF STUDIES EVALUATING VARIOUS INTRA-ARTERIAL TREATMENT MODALITIES FOR LIVER-DOMINANT BREAST CANCER METASTASES

Treatment Modality Studied	Authors	No. of Patients	Agent Utilized	Toxicities	Disease Control	Median Overall Survival
Conventional transarterial chemoembolization	Cho et al[7]	10	Doxorubicin, gemcitabine/cisplatin, cisplatin, oxaliplatin	70% with nausea/vomiting/abdominal pain	40% (RECIST)	12 mo*
	Vogl et al[8]	161	Mitomycin C ± gemcitabine	28% had symptoms requiring prolonged hospital stay (2–7 days)	64% (RECIST)	32.5 mo†
	Eichler et al[9]	43	Gemcitabine	56% with grade 1–2 nausea/vomiting	49%	10.2 mo
Drug-eluting embolic transarterial chemoembolization	Martin et al[10]	40	Doxorubicin, 100–300-µm beads‡	17% overall rate of toxicities (≥ grade 3 toxicities included nausea/vomiting, esophagitis)	57.5% (mRECIST)	47 mo
	Lin et al[11]	23	Doxorubicin, 70–150-µm beads	35% with ≥ grade 3 toxicities	83% (RECIST)	17 mo
Y-90 transarterial radioembolization	Haug et al[12]	58	Resin	12% grade 3–4 biliary or hepatic toxicities	88% (RECIST)	11 mo
	Cianni et al[13]	52	Resin	3.8% REILD, 3.8% gastritis	91.4% (RECIST)	11.5 mo
	Saxena et al[14]	40	Resin	40% grade 1/2 toxicities	71.1% (RECIST)	13.6 mo
	Gordon et al[15]	75	Glass	7.6% grade 3 clinical toxicities, 5.9% hyperbilirubinemia	98.5% (RECIST)	9.3 mo
	Fendler et al[16]	81	Resin	< 10% grade 3 or higher	52%–61% response§	8.2 mo
	Pieper et al[17]	44	Resin	2% cholecystitis, 2% duodenal ulcer, 30% ascites	71.8% (RECIST)	6.1 mo
	Bangash et al[18]	27	Glass	11% grade 3 biliary toxicity	39.1% ORR, 52.1% SD (WHO)	6.8 mo¶, 9.2 mo‖

Abbreviations: mRECIST, modified Response Evaluation Criteria In Solid Tumors; ORR, objective response rate (complete response + complete response); PET, positron emission tomography; RECIST, Response Evaluation Criteria In Solid Tumors; REILD, radioembolization-induced liver disease; SD, stable disease; WHO, World Health Organization; Y-90, yttrium-90.

*Reported mean overall survival.

†Conventional transarterial chemoembolization was combined with ablation.

‡Additional beads were administered at sizes per the discretion of the operator.

§Response based on > 30% decrease in 18F-fluorodeoxyglucose PET/CT avidity and/or decrease of CA 15-3 serum markers.

¶For patients with Eastern Cooperative Oncology Group 0.

‖For patients with < 25% tumor burden.

studies of women with breast cancer hepatic metastases have been reported (Table 1).[10,11] The first study evaluated 40 women who underwent DEE-TACE for the treatment of breast cancer hepatic metastases.[10] The tumor response was 57.5% using modified Response Evaluation Criteria In Solid Tumors (mRECIST) criteria at 3 months, and median overall survival was 47 months. The second study reported on 23 women, with a disease control rate of 83% using RECIST.[11] There were 35% grade 3 or higher toxicities, which included asthenia, anemia, thrombocytopenia, and liver toxicity. The median overall survival was 17 months.

Yttrium-90 Transarterial Radioembolization

TARE employs 20–30-µm microspheres loaded with yttrium-90 (Y-90). The microspheres are made of resin (SIR-Spheres, Sirtex Medical Inc.) or glass (TheraSphere, BTG International). Their use is off-label for patients with metastatic breast cancer. Y-90 decays at the level of the tumor, producing β radiation with a mean penetration of 2.5 to 11 mm from the microsphere. Radioembolization has the most robust data for the treatment of hepatic-dominant breast cancer (Table 1).[12-18] A total of 377 patients were evaluated at six centers, and the majority of centers utilized resin microspheres. The relative rate of toxicities was low and ranged from 4% to 40%, but the majority of toxicities were grade 1 or 2. Response rates ranged from 26% to 63.2%, and median overall survival rates ranged from 6.1 to 13.6 months.

DISCUSSION

Metastatic breast cancer is a significant clinical problem, and once women develop liver metastases, their overall prognosis is poor.[4,5] Most patients are not candidates for surgery or ablation due to distant metastatic implants. A small study demonstrated that more than half of the women (52%) who underwent targeted resection and/or ablation for liver metastases were found to have extrahepatic disease on follow-up imaging.[19] Despite undergoing surgery, 87% of these patients still required concurrent systemic therapy.

Although no level 1 data exist for liver-directed therapy (LDT) in hepatic-dominant breast cancer metastases, studies have shown that LDT embolotherapies can stabilize disease with minimal toxicities. Despite the varied reported responses, at least 50% of women demonstrated a response to therapy after LDT. However, these responses were seen in women who had limited or no additional treatment options and had already undergone multiple previous systemic therapies that had failed.[15] The overall impact of embolotherapies on survival is still unknown, and it is difficult to assess due to the varied timing of therapies and patients' history of multiple lines of prior chemotherapy.

The benefits of these therapies do outweigh the risks. Toxicities were minimal and mild (grade 1–2) in most cases, with 12% reported as grade 3 or higher.[12] As another benefit, LDT can often be performed as an outpatient procedure, causing little disruption to the patient's daily routine.

Irrespective of treatment modality, the current data offer some guidance as to which patients might benefit most from LDT. Patients with < 25% tumor burden have longer median overall survival (9–14 months) than those with > 25% tumor burden.[13-16] Thirty-day mortality was seen after LDT only in patients with > 25% tumor burden. The presence of stable extrahepatic disease did not correlate with worsened overall survival, indicating that patients with extrahepatic metastases may benefit from targeted liver therapy. Lastly, as ECOG (Eastern Cooperative Oncology Group) performance status declined, overall survival also declined. At a more granular level, when comparing the modalities, TACE had the highest associated toxicities (although mild), whereas TARE had the lowest. Tumor response rates were better with TARE as compared with cTACE or DEE-TACE. This could be due to the different mechanism of action between TACE and TARE. TACE induces anoxia/hypoxia, producing ischemia; TARE is microembolic, with the microspheres acting as a carrier of a radioisotope. Breast cancer liver metastases, unlike primary liver cancer, are hypovascular. Therefore, TACE may not be as effective due to mechanism of cell death and/or tumors that may be chemoresistant.

As with all therapies, patient selection is critical to understanding when to utilize LDT in the course of treatment. It is crucial that these decisions are made with the aid of a multidisciplinary team to ensure that the most reasonable modality is utilized and the timing of therapy is optimized.

Because of the limited toxicities, LDT can also be used as an adjuvant therapy. It has the benefit of treating the liver disease while allowing the patient to receive additional systemic therapies, if needed. A recent phase 1 study demonstrated that TARE can safely be given concomitantly with systemic therapy (capecitabine).[20] Other such studies are also currently underway, combining LDT with systemic therapy. Additionally, immunotherapy is currently being employed in most cancer types. Traditional radiation therapy has been shown to have an abscopal effect.[21] Studies are underway to examine whether the abscopal effect can enhance the treatment response to immunotherapies. Because external beam

hepatic radiation has so many associated toxicities,[22] utilizing TARE may be more advantageous due to fewer associated side effects.

CONCLUSION

The treatment of invasive breast cancer requires multiple therapeutic modalities and a multidisciplinary team approach. LDT has been proven to improve overall survival while maintaining a patient's quality of life in both primary and secondary liver cancer. Studies to date have included more than 650 women with hepatic breast cancer metastases who have been treated with LDT, with limited associated toxicities. Based on these data, more than 50% of women will respond to LDT, and fewer than 12% will experience toxicities grade 3 or higher. Therefore, LDT should be considered a safe and effective adjuvant therapy for the treatment of hepatic-dominant breast cancer metastases. ■

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