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BRIEF REPORT

Optimal outcomes for liver-dominant metastatic breast cancer with transarterial chemoembolization with drug-eluting beads loaded with doxorubicin

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Abstract The purpose of this study was to evaluate the efficacy of image-guided delivery of locoregional chemotherapy to breast cancer hepatic metastases using doxorubicin-loaded drug-eluting beads (DEBDOX). An IRB-approved multi-center, prospective, open, non-controlled repeat treatment registry to investigate the safety and efficacy of doxorubicin microspheres in the treatment of patients with unresectable liver metastasis from breast cancer was reviewed. Statistical analysis was performed with differences of $P < 0.05$ considered significant. About 40 patients with metastatic breast cancer (MBC) to the liver underwent a total of 75 image-guided procedures with hepatic arterial drug-eluting beads loaded with doxorubicin (DEBDOX). Treatment was well tolerated with a total of eight patients sustaining 13 adverse events within the 30 days of each treatment session. All adverse events were either a grade I or grade II in toxicity. After a median follow-up of 12 months in all patients, the hepatic progression-free survival was a median of 26 months and overall survival was a median of 47 months. The treatment of hepatic metastasis from MBC using DEBDOX is an effective local therapy with very high response rates and a very safe toxicity profile. In comparison to chemotherapy alone, consideration of hepatic-directed therapy is warranted in patients with liver-dominant metastatic disease.

Keywords Metastatic breast cancer · Liver-directed therapy · Chemoembolization · Doxorubicin

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Introduction

The presence of hepatic metastases still remains a clinically significant and therapeutically frustrating problem in clinical oncology secondary to the sanctuary effect of the liver in relation to systemic chemotherapy. Liver metastases still remain a major cause of morbidity and mortality in patients with malignant tumors of different origins. Breast cancer liver metastases usually indicate the presence of hematogenously disseminated cancer with a very poor prognosis [1], with an overall incidence during the lifetime of a patient at 30–50% [2–4].

Secondary to this high incidence, minimally invasive therapy methods, such as radiofrequency ablation (RFA), laser-induced thermotherapy, transarterial chemoembolization (TACE), and drug-eluting bead therapy, have been used for effective treatment of liver metastases from breast cancer [5, 6]. In appropriate patients, locoregional

treatments, including hepatic resection, RFA, and now drug-eluting bead chemotherapy, have become potential treatment options in the management of this disease [7–13]. TACE is a local catheter-based minimally invasive therapeutic option for unresectable liver tumors, and is defined as a selective administration of chemotherapy usually combined with embolization of the vascular supply of the tumor [6]. Ideally, a locoregional treatment with limited systemic exposure and a reduced side effect profile when compared with systemic chemotherapy could be included as a part of the strategy when treating breast cancer hepatic metastases. In contrast to TACE, drug-eluting hepatic arterial chemotherapy is a regional therapy that has been effectively offered in patients with unresectable hepatocellular cancer and unresectable colorectal liver metastasis [14, 15]. It has the ability to deliver high-dose chemotherapy directly to the liver tumors with minimal systemic chemotherapy effects [16–18]. Established pharmacokinetic studies have demonstrated minimal to no systemic exposure with the use of at least 450 mg of doxorubicin when delivered with the drug-eluting bead device [14, 19]. Our group has published early safety and efficacy data about this device in 15 patients with metastatic breast to the liver who underwent a total of 32 treatments with image-guided hepatic arterial drug-eluting beads loaded with doxorubicin (DEBDOX) [20]. Treatment was well tolerated, with a total of six patients sustaining 12 adverse events within the 30 days of each treatment session. All adverse events were either a grade I or grade II in toxicity. After a median follow-up of 12 months, response rates have been 100% at 3 months, 90% at 6 months, and 65% at 12 months with a median overall survival of 15 months from time of treatment and 26 months from time of metastatic disease. We concluded that the treatment of hepatic metastasis from metastatic breast cancer (MBC) using DEBDOX is safe and effective with very high response rates and a very safe toxicity profile.

This study was performed on a relatively large number of patients to determine the response and survival rates of patients who undergo hepatic arterial therapy of breast cancer liver metastases and to compare the effectiveness to current chemotherapy regimens.

Materials and methods

An IRB-approved, prospective, multi-institutional, open, non-controlled repeat treatment registry of 808 patients undergoing 1,345 treatments for primary or secondary cancers in the liver was evaluated from January 2007 to July 2011 [21, 22]. Patients presenting with liver-dominant MBC to the liver were treated with doxorubicin drug-eluting beads. The registry was initiated to satisfy the strict criteria for critically appraising the quality of a registry study with (1) a well-described patient population; (2) hypothesis generating and answering questions; (3) high-quality data, with good quality control; (4) independent assessment of outcomes; (5) good, clinically relevant follow-up with minimal loss of patients; and (6) comparable patient evaluation across all institutions participating [21].

Patients were included for therapy if they were 18 years of age, of any race or sex, had radiologic and histologic proof of MBC to the liver by percutaneous biopsy, were able to give informed consent, and were eligible for treatment. Patients must have had an ECOG performance status score of less than or equal to 2 with a life expectancy of greater than or equal to 3 months, and non-pregnant with an acceptable contraceptive in pre-menopausal women. Exclusion to therapy was contraindication to angiographic and selective visceral catheterization, significant extrahepatic disease representing an eminent life-threatening outcome, greater than 75% of hepatic parenchymal involvement, severe liver dysfunction, pregnancy, and severe cardiac co-morbidities. Only patients with liver-dominant disease (defined as greater than 50% of the overall total disease burden) were considered for treatment.

Standard pre-therapy evaluation of patients with MBC included at least a three-phase CT of the abdomen and pelvis and chest roentgenogram at least 1 month or less before treatment, with the use of PET scanning depending on the institution and the availability of the technology for use. Prior systemic chemotherapy of any type and duration was allowed and was recorded.

Patients were followed for any treatment-related adverse experiences for 30 days after each treatment and monitored for survival for 2 years. All adverse events were recorded per standards and terminology set forth by the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, Version 3.0. Follow-up assessments included a tri-phase CT scan of the liver within at least 1–2 months from the treatment completion with the evaluation of the enhancement pattern of the target lesion and tumor response rates measured according to modified RECIST criteria [23].

Image-guided infusion technique

As per the Society of Interventional Radiology Clinical Practice guidelines, standards for reporting techniques and terminology are used [24]. According to the standardization of terminology and reporting criteria by Brown et al. [6], the DEBDOX device does not fit into either as a "chemoembolization" (aqueous chemotherapy is not infused) or as an "embolization" (because chemotherapy is

delivered); thus, we have used the terminology of "precision chemoembolization" to define this device at this present time.

Diagnostic angiography was performed by the interventional radiologist and consisted of selective celiac and superior mesenteric arteriogram to evaluate the hepatic arterial anatomy. For tumors near the periphery of the liver, evaluation of potential extrahepatic supply to the tumors, such as the inferior phrenic, gastroepiploic, and internal mammary arteries, was performed. Once it was evaluated for the degree of hepatic tumor perfusion, the next step in evaluation was to limit any type of extrahepatic perfusion of the treatment. The most common branches that will lead to extrahepatic disposition of treatment are the right-gastric and the gastroduodenal arteries, which are either controlled before infusion with coil embolization or at a minimum with distal catheter placement.

Defining the amount of liver disease was integral to defining both the number of treatments and catheter position and the therapy that would be performed. For finite numbers of lesions—defined as less than four lesions—a treatment cycle was planned for a minimum of two dosing schedules of at least 100–150 mg of DEBDOX. The drug was distributed in two 2-cc bead vials, with the amounts per vial determined per the physician's judgment. Bead sizes of 100–300, 300–500, or 500–700 μm could be selected. Treatment intervals were planned for every 4–8 weeks, which allowed for extending the interval if the toxicity is seen. Either two to three treatment cycles were planned based on the extent of liver involvement, with a repeat scan every 3 months from the initial treatment cycle to evaluate response as well as planned re-treatment. A *treatment cycle* is defined as treatment of all liver disease. A *treatment* is hepatic arterial therapy to one single lobe, which could also be a treatment cycle if a patient has only unilobar disease.

For diffuse disease, a minimum of four-dosing schedule is planned. Again depending on the extent of tumor burden and the extent of hepatic parenchymal reserve, 100–150 mg of doxorubicin is loaded into two 2-cc bead vials. At least two treatments per lobe are planned on a 3–4-week dosing schedule, extending the interval if toxicity is seen. A repeat CT scan is planned for 3 months from the first dose to evaluate tumor response. For example, if patients present with bilobar disease, they would receive a first bead treatment to right lobe, then 3 weeks later a second bead treatment to the left lobe, then 3 weeks later a third bead treatment to the right lobe, and then again 3 weeks later to the left lobe. The decision on bead size was up to the treating physicians' judgment based on their initial experience with particle size and the degree of stasis that was planned to be delivered at the end of the treatment. The reason for lobar infusion is based on the desire for drug delivery and less on inducing stasis in patients with multifocal lobar disease that is not amenable to superselective delivery.

Peri-procedural medications, including pain medications, antibiotic prophylaxis, corticosteroids, and proton pump inhibitors, were all prescribed at the physician's discretion.

The mixing of DEBDOX was performed with non-ionic contrast (approximately 50/50 dilution) before injection. The minimum recommended loaded bead-to-contrast mixture is approximately 10.0 cc to ensure smooth catheter delivery. After appropriate mixing and removal of the un-eluted supernatant, a microcatheter is then placed based on the extent of liver disease. For a finite number of lesions, the microcatheter is selectively placed (selective or superselective based on tumor size and location) for the first bead vial (a 100–300-μm size) with initial infusion and then pulled back to a lobar infusion for the second bead vial of the size choice (based on physician discretion). For diffuse disease, a lobar infusion using a microcatheter into either the right or left artery, depending on the bulk of disease, is performed with the bead size the physician deems most suitable.

Drug preparation

All bead therapies were performed with the DC/LC^{TM} bead microsphere (Drug Eluting Bead [DEB]; www.biocompatibles.com, Biocompatibles UK, Surrey, UK). The saline suspension in the DC/LC^{TM} bead microsphere was removed and the beads were mixed with doxorubicin solution at a dose of 75 mg per 2 ml at least 4 h before the procedure, depending on the dose that was planned to be delivered.

Data were censored at the last recorded patient contact if an endpoint was not reached. Recurrence was also evaluated using PET scan. A recurrence was the re-occurrence of viable tumor by radiologic CT criteria of a vascular mass. In the event of subsequent hepatic therapy for recurrence of disease, only the first procedure was used for the purposes of this study. Chi-square, Student's *t*-test, and Mann–Whitney's *U*-test for nominal, continuous, and ordinal variables were used to evaluate the association of independent variables to surgical complications. Proportional hazards analysis was performed on all variables found significant by univariate analysis. Relative risk (RR) with 95% confidence intervals was calculated as a measure of association. Differences of $P < 0.05$ were considered significant. Statistical analysis was performed using JMP software (JMP; SAS Institute Inc., Cary, NC).

Also, in an attempt to evaluate these results with the use of DEBDOX to other therapies in MBC, we performed a

search using PubMed and search terms *metastatic breast cancer* that yielded more than 28,000 results, more than 16,000 of which were published in the last 10 years. Using *metastatic breast cancer liver* as search terms produced 1,363 results for the last 10 years (1999 to present). When results are limited to non-review clinical trial literature in humans, also written in English and containing an abstract, the results were 92 peer review publications. Eighteen of these manuscripts were excluded for the lack of relevance after further examination. Of the remaining publications identified, 70 referred to phase I–III trials of systemic chemotherapy, with only 26 of those manuscripts identifying any patients with liver metastasis. From these 26 publications, only 12 identified selective outcomes among MBC patients according to exact site of metastasis.

Results

A total of 40 patients who had undergone either total mastectomy or partial mastectomy with radiation therapy were treated with hepatic arterial bead treatment. The median age was 60, with a range of 38–83 with 100% being female (Table 1). All patients who presented for hepatic arterial evaluation were of a good to exceptional performance status. Of the 40 patients, 11 had undergone either hepatic resection or hepatic ablation for what was felt to be focal disease and then subsequently recurred. A majority of all patients had low-volume disease with less than 25% liver involvement, but with a miliary multifocal type of disease. The cumulative sum target lesion was 7.6 cm, although tumor diameters among the patients ranged widely from 2.7 to 27.1 cm.

A majority of patients did have focal extrahepatic disease that was stable on their current chemotherapeutic regimen and they were referred for hepatic arterial therapy because of either liver refractory disease or because of a desire for consolidative therapy to the liver. All patients had received multiple first-, second-, and even third-line standard of care systemic chemotherapy, as well as receptor antagonist therapy before undergoing hepatic arterial therapy.

Of the 40 patients who were treated, they underwent a total of 75 bead treatments with 73 of these treatments being with doxorubicin drug-eluting bead therapy (Table 2). Two patients were treated with Yttrium-90 therapy to the right lobe of the liver because of the small miliary disease in that lobe with the left lobe treated with doxorubicin treatments. The remaining patients received only doxorubicin bead treatments. The median number of treatments was two, with a cumulative total hepatic exposure being 250 mg; some patients received a maximum total dosage of 550 mg. Pre- and post-MUGA evaluating left-ventricular ejection fraction did not change in patients while undergoing hepatic arterial therapy, with a median range in differences of 1.5% (range negative 3% to positive 3.8%). A majority of patients were treated with concurrent chemotherapy or receptor antagonist with the doxorubicin drug-eluting bead therapy performed on the off week if they were receiving systemic chemotherapy. Doxorubicin was performed in combination with receptor therapy such

Table 1 Clinical characteristics of breast cancer patients with liver metastases treated with doxorubicin LC beads

Characteristics	$N = 40$
Age (years) (median, range)	60 (38–83)
Gender	Female (100%)
Ethnicity	
Caucasian	36 (83%)
African-American	1 (4%)
Hispanic	2 (8%)
Asian/Pacific Islander	1 (4%)
Karnofsky performance score	
80–100%	38 (92%)
50–70%	2 (8%)
Prior liver surgery	
Hepatic resection (lobectomy)	6
Radiofrequency ablation	5
Liver involvement ($n = 21$)	
<25%	30 (62%)
26–50%	6 (24%)
>50%	4 (14%)
Number liver tumors ($n = 23$)	
Radiologically distinct number (median, range)	34 (4, 1–25)
Numerous	6
Sum target lesion(s) size (median, range)	7.6 cm (2.7–27.1 cm)
Extrahepatic disease	22 (57%)
Site: bone	16
Lung	3
Brain	2
Pancreas	1
Previous chemotherapy	
Taxanes	24
Anthracyclines	15
Gemcitabine	10
Cyclophosphamide	7
ER antagonists/aromatase inhibitor	7
Avastin	5
Other	9

ER estrogen receptor

Other chemotherapy previously given: vinorelbine (3), carboplatin (2), capecitabine (9), lapatinib (3), herceptin (5)

Table 2 Bead catheter infusion outcomes

	$N = 75$ total treatments
Bead treatments	
Doxorubicin LC beads	73
Therapheres	1
Sir-spheres	1
Number of bead courses	2 (range 1–6)
Technical success	100%
Doxorubicin dosage delivered (median, range)	100 mg (8–150 mg)
Total hepatic dose exposure	250 mg (150–550 mg)
Complication (%)	(13 of 75 = 17%)
Extrahepatic infusion	1
Concurrent chemotherapy[a]	
Bisphosphonates	18
ER antagonists/aromatase inhibitors	25
Herceptin	10
Taxanes	7
Carboplatin	2
Ixempra	7
Capecitabine	11

[a] Greater than 40 patients because some patients were on multiple therapies at the time of bead treatment

Table 3 Bead infusion–related morbidity (13 adverse events in 75 treatments)

Adverse event	All grades (%)	Severe grades[a] (%)
Nausea	11	3
Vomiting	8	3
Fever	8	0
Liver dysfunction/failure	6	0
Hepatic necrosis	3	0
Pain	14	0
Constipation	3	0
Hemoptysis	3	0
Esophagitis	3	3

[a] Defined as grade 3 or higher

as Herceptin and the established estrogen receptor antagonist. Of the total 75 treatments performed, 13 had some form of adverse events related to morbidity of the hepatic arterial bead treatment (Table 2).

The most common adverse events were nausea, vomiting, and pain that did require additional oral narcotics after discharge (Table 3). There was one episode of extrahepatic infusion into the gallbladder that required a laparoscopic cholecystectomy 6 weeks post-hepatic arterial bead treatment. The majority of all adverse events were mild. Nausea and vomiting were defined as severe if it required a patient to stay greater than the 23-h admission or required a re-admission for nausea and vomiting following discharge after completing hepatic arterial therapy.

In a review of response rates, the initial overall response at 3 months was 58%, with the overall response rate at 6 months being 50% and maintaining that 50% response rate at both 9 and 12 months, with a slightly smaller response rate at greater than 18-month follow-up. A review of data indicated a median overall survival of 47 months, ranging from 9 to 78 months from the time of initial diagnosis (Table 4). The median progression-free survival (PFS) was 17 months. Hepatic-specific PFS was 26 months; extrahepatic PFS was 14 months. Table 4 summarizes 1-year PFS, hepatic-specific PFS, and extrahepatic PFS.

Discussion

Metastatic breast cancer occurs in approximately 25–40% of patients who are diagnosed with breast cancer [25]. Advances have been made in the treatment of early breast cancer that have improved overall survival and time to progression, including the use of anthracyclines with taxanes [26]. However, a diagnosis of MBC is generally considered to carry a poor prognosis [27]. There are many treatment options that can be considered for MBC and these depend on the location and extent of metastasis, the hormone receptor status of the tumor, Her-2/neu status, and previous treatments given [28]. The response rate to treatment of MBC also drops with each line of failed treatment. Tumors have initial response rates of between 30 and 65% and PFS of up to 11 months. This drops dramatically to as low as 10–15% response rates and PFS of only 3–4 months with second, third, and even fourth lines of treatment [28]. In addition, response rates are generally lower for patients with MBC treated initially with anthracycline/taxane regimens as they are often resistant to further treatment with these drugs. Recently, capecitabine has been investigated as a new therapy, either alone or in combination with other chemotherapy agents, for taxane-resistant tumors with response rates between 15 and 20% [29]. Ixabepilone is another new drug therapy that has proved effective [30].

Liver metastasis from breast cancer is also quite common, occurring in approximately 15% of those patients with MBC [31]. Metastatic disease confined to the liver occurs in about 4–5% of patients with MBC [31, 32]. Liver resection is possible in a proportion of patients with disease in defined localized areas confined to the liver, or where extrahepatic metastatic disease is medically stable (Table 5). Surgical resection of metastases can also

Table 4 Response rates for 40 patients evaluated at follow-up

Response	3 months ($n = 40$)	6 months ($n = 40$)	9 months ($n = 38$)	12 months ($n = 36$)	≥18 months ($n = 32$)
Complete response	3	9	8	6	4
Partial response	20	11	9	11	8
Stable disease	13	12	12	6	3
Progression of disease	4	6	9	4	6
Died of disease	0	1	2	4	5
Died of other cause	0	1	0	0	1
Time not reached	0	0	0	2	5

Progression-free, hepatic-specific, and overall survival

Survival	Median (months)
PFS	17
Hepatic	26
Extrahepatic	14
Overall survival	47

Table 5 Surgical resection of breast cancer liver metastases—selected patients

Author	Year	# pts	Liver-dominant disease (yes/no)	Chemotherapy reported	Overall survival (months)	Comments
Selzner et al. [40]	2000	17	Yes	Neo-adjuvant high-dose chemo	24	Surgical resection
Yoshimoto et al. [10]	2000	25	Yes	24 post-op chemo	34	Surgical resection
Carlini et al. [41]	2002	17	Yes	Post-op chemo	53	Surgical resection
Elias et al. [9]	2003	54	Yes	25 pts HAIC	34	Surgical resection; HAIC significantly reduced liver recurrence but did not affect survival; survival better if HR + ve
Vlastos et al. [8]	2004	31	Yes	87% pre/post-op systemic chemo	25	Surgical resection
Sakamoto et al. [42]	2005	34	Yes	NR	36	Surgical resection
d'Annibale et al. [43]	2005	18	Yes	9 adjuvant chemo	36	Surgical resection
Adam et al. [7]	2006	85	Yes	NR	32	Surgical resection
Adam et al. [44]	2006	454	Yes	NR	45	Surgical resection; part of retrospective analysis of 1452 pts with liver mets of non-colorectal non-neuroendocrine origin
Lubrano et al. [33]	2008	16	Yes	All previous systemic chemo	42	Surgical resection
Caralt et al. [45]	2008	12	Yes	NR	36	>24 months interval between primary and liver mets had signif. better survival
Furka et al. [46]	2008	17	Yes	NR	19	

NR not reported

No response rate as all surgeries considered complete and potentially curative. Median overall survival = 36 months

improve survival [33]. Patient selection is important to both morbidity and outcome of these procedures, but can provide improved overall survival from only a few months with systemic treatment alone to more than 36 months with resection. Other liver-directed therapies have been used to palliate liver metastasis from breast cancer. TACE is designed to directly infuse metastatic tumors with chemotherapy treatments and at the same time block tumor blood

Table 6 Treatment of breast cancer liver metastases by radiofrequency ablation (RFA), transarterial chemoembolization (TACE), or other directed liver treatments

Author	Year	# pts	Liver-dominant disease (yes/no)	Chemotherapy reported	Response rates	Overall survival (months)	Comments
Li et al. [47]	2005	48	Yes	TACE vs. systemic chemo (unspecified)	35.7% TACE vs. 7.1% chemo		$N = 28$ TACE, $n = 20$ chemo; 3 yr survival: 13%TACE vs. 0% chemo
Giroux et al. [48]	2004	8	Yes	TACE	62.5%	20	Mean survival from primary diagnosis = 49 months
Vogl et al. [49]	2003	25	Yes	TACE (mitomycin) + LITT	56%	25	Neoadjuvant TACE followed by laser-induced thermotherapy (part of larger trial including other primary tumor sites
Lawes et al. [13]	2006	19	Yes	RFA			41.6% survival at 30 months
Amersi et al. [35]	2006	9	Yes	RFA		39	Pt of larger trial in pts with liver mets from multiple primary sources
Meloni et al. [50]	2009	52	Yes	RFA		42	5 yr survival 32%
Ikeda et alkeda [51]	1999	28	Yes	Adriamycin + 5-FU	54%	25	Continuous intra-arterial chemo
Camacho et al. [52]	2007	10	Yes	Intra-arterial paclitaxel	70%		Pilot study
Maes et al. [53]	2008	30	Yes	Intra-arterial mitomycin C	33%	7	All pts had extensive liver mets; liver only mets did better
Gulec et al. [54]	2007	4	Yes	Y-90 Sir-spheres	60%		Pt of larger study—40pts
Visonneau et al. [55]	2000	15	No	Tall-104 T-cells	33%		Phase I toxicity trial

LITT laser-induced thermotherapy; *5-FU* 5-fluorouracil

supply (Table 6). This technique has been extensively used in the treatment of colorectal liver metastases [34], but has not been well-studied for breast cancer liver metastasis (Table 6). RFA has also been used for treatment of liver metastases of many primary sources, as well as primary hepatocellular carcinoma [35]. As with TACE, RFA is useful in selected patients with localized metastatic liver disease, and is also being investigated more recently as an adjuvant treatment [36]. Other locoregional therapies have also been tried, including intra-arterial infusion of chemotherapy into the liver of patients with MBC.

Most of these liver-directed treatments are used as adjunct therapies, and systemic chemotherapy regimens remain the main treatments given to MBC patients with liver disease [37]. Most of the studies investigating potential new chemotherapy agents or dosing strategies of systemic chemotherapy drugs do not differentiate among sites of metastatic disease. It is, therefore, difficult to determine the efficacy of systemic treatments. Tumors metastasized to bone respond very differently from tumors metastasized to liver or brain. Without data from trials that separate out response rates and survival according to metastatic location, and possibly other factors such as hormone receptor status, it is impossible to tailor treatments for MBC patients and so it is unlikely that response rates and survival will improve further.

The use of systemic chemotherapy in MBC still remains the standard of care. However, response rates with these treatments varied from 11.6% [38] to nearly 83% [39], with many identifying better than expected response rates for liver metastases (Table 7). A selection of other studies investigating systemic chemotherapy that identified site of metastasis or stratified patients and outcome in some way are listed in Table 7. The studies listed in Tables 7 and 8 suggest that it may be possible to identify specific treatments that are more effective for certain MBC patients based on the location and extent of metastatic disease. When our data presented using DEBDOX for patients with liver-dominnat MBC were compared with the current standard of care treatment, there are potential improvements in the outcome that may translate with the use of hepatic-targeted therapy.

One of the greatest challenges in managing patients with MBC is establishing an appropriate treatment with optimal response while allowing for adequate quality of life during the treatment. Surgical resection allows for the maximum response rates, but the number of patients that are eligible for resection and/or ablation based on a finite number of

Table 7 Systemic chemotherapy trials specifically investigating effects on liver metastases (12 studies)

Author	Year	# pts	Liver-dominant disease (yes/no)	Chemotherapy reported	Response rates	Overall survival (months)	Comments
Mavroudis et al. [56]	1999	52	No	Docetaxel/gemcitabine	54%		Second-/third-line treatment; liver mets and other responded
Baselga et al. [57]	1999	46	No	Trastuzumab	11.6%		Weekly for 10 weeks; Her2 +ve tumors; liver mets and others responded
Alexandre et al. [58]	2000	825	No	Docetaxel	22.9%	9.8	Liver mets and others responded
Sanchez-Rovira et al. [39]	2001	41	No	Gemcitabine/ doxorubicin/paclitaxel	82.9%	26.2	27pts also +G-CSF; liver mets and others responded
Atalay et al. [59]	2003	49	No	A:doxocycline versus paclitaxel; B: doxocycline/cyclophos versus doxocycline/ paclitaxel; analysis included liver mets alone (LMA) and total pts with LM	LMA:A-44%, B-23% LM:A:29%, B-30%	LMA:A-22.7, B-27.1 LM:A-14.2, B-16.8	Analysis of two EORTC Phase III trials; LM = 48%; LMA = 9% of total, 18% of those with LM
Mouridsen et al. [60]	2004	907	No	Letrozole versus tamoxifen			Phase III trial—letrozole 025; subanalysis of outcome in pts with liver mets only/other visceral mets/non-visceral mets
Iba et al. [61]	2004	15	No	Oral 5-DFUR (pro-5-FU)/cyclophosphamide			2pts with liver mets—both responded
Stathopoulos et al. [62]	2005	48	Yes	Docetaxel + irinotecan	52%		Liver metastases most responsive
Pentheroudakis et al. [63]	2006	500	Yes	Anthracycline ± taxane (88%) Second-line treatment	34% 16%	16.3	5 year survival 8.5%; retrospective breast cancer registry analysis of pts with liver mets
Nishimura et al. [64]	2008	74	No	Trastuzumab versus Trastuzumab + chemo (unspecified)	65% trast alone versus 86% trast + chemo		Pts with liver mets: TTP 5.7 months trast alone versus 15.9 months trast + chemo
Er et al. [65]	2008	132	Yes	Anthracyclines (62%); +taxane (38%);	66.4%	25	Extent of liver mets, liver function and performance status related to survival
Tanabe et al. [66]	2009	48	No	Mitomycin C + methotrexate	24% (31% liver mets)		Previous anthracycline/taxane

TTP time to progression, *5-FU* 5-fluorouracil, *G-CSF* granulocyte colony-stimulating factor

liver metastasis and liver-only disease is small. However, with the advent of laparoscopic resections, the limited morbidity and minimal quality of life effects have been established and should be considered in the appropriate population. Hepatic arterial therapy or TACE has been effective to be effective as long as the adverse events are minimal and allows for the concomitant use of some form of systemic therapy because it is well established that some systemic exposure does occur with conventional TACE. We have demonstrated here that with the use of DEBDOX, the adverse event rate is minimal when the appropriate patients are selected with the appropriate technique, with the ability to deliver continued doxorubicin without any cardiac effects.

Thus, in conclusion, the treatment of hepatic metastasis from MBC using DEBDOX is an effective local therapy with very high response rates and a very safe toxicity profile. In comparison to chemotherapy alone, consideration of hepatic-directed therapy is warranted in patients with liver-dominant metastatic disease.

Table 8 Recent studies investigating chemotherapeutic treatments for metastatic breast cancer (MBC)—preference for those identifying pts with liver mets

Author	Year	# pts	Liver-dominant disease (yes/no)	Chemotherapy reported	Response rates	Overall survival (months)	Comments
Kalbakis et al. [67]	2001	41	No	LV + 5-FU + cyclophsoph amide	26.9%	13	MBC pts with anthracycline/taxane pretreatment
Airoldi et al. [68]	2006	40	No	Gemcitabine + oxaliplatin	65%	13	37/40 visceral mets; 2 pt liver mets alone; 14 pts liver and multiple organs; all pts pretreated with anthracycline/taxane
Delozier et al. [69]	2006	47	Yes	Oxaliplatin + vinorelbine + 5-FU	34.8%	18.8	68% liver mets
Blum et al. [70]	2007	181	NR	Albumin-bound paclitaxel	15%	9	All pts pretreated with taxanes; two dosing strategies used
Onyenadum et al. [71]	2007	48	Yes	Mitoxantrone + vinorelbine	29.5%	13	64% liver mets
Thomas et al. [72]	2007	752	No	Ixabepilone + capecitabine versus capecitabine	I + C: 35%; C:14%		Randomized control trial phase III
Garin et al. [73]	2008	50	No	Premetrexed + carboplatin	54%		Includes 30% pts locally advanced disease, 70% mets
Campora et al. [74]	2008	65	No	Docetaxel	45%		25 pts with liver mets
Tan et al. [75]	2009	64	NR	Irinotecan + docetaxel	34%		Phase II trial; All previously treated with anthracycline/taxane
Polyzos et al. [76]	2009	28	NR	Oxaliplatin + capecitabine	32%	10	All previously treated with anthracycline/taxane
Tubiana-Mathieu et al. [77]	2009	49	NR	Vinorelbine + capecitabine	51%	29.2	HER2 negative; first-line treatment
Sparano et al. [78]	2009	751	NR	Docetaxel (D) versus pegylated liposomal doxo (PLD) + doxo	26%(D) versus 35% (PLD/D)	No difference between groups	Phase III; previous anthracycline treatment
Yardley et al. [79]	2009	37	NR	Gemcitabine + trastuzumab	30%		HER2 + ve mets

LV leucovorin, *5-FU* 5-fluorouracil

Conflict of interest None.

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