Original Article

Chemotherapy for breast cancer progresses to liver metastases after surgery and systemic treatment

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Background: This study aims to evaluate the effectiveness of hepatic arterial infusion chemotherapy/portal vein infusion chemotherapy (HAIC/PVIC), transcatheter hepatic arterial chemoembolization (TACE) and transcatheter arterial embolization (TAE) for unresectable breast cancer liver metastases (UBCLM).

Methods: The present study included 57 patients. These patients were randomly divided into three groups (n=19, each): HAIC/PVIC group, TACE group and TAE group. Patients in the HAIC/PVIC group were treated with the same systemic chemotherapy regimen previously received by infusion through an intra-arterial and portal vein catheter. Patients in the TACE group received cyclophosphamide, epirubicin and 5-fluorouracil, and embolization. Patients in the TAE group were only treated with embolization.

Results: The median number of treatments was 6 (range, 3–13) in the HAIC/PVIC group, 5 (range, 4–9) in the TACE group, and 6 (range, 4–8) in the TAE group. The 1-, 2- and 3-year survival rates for these groups were 18/19 (94.7%), 14/19 (73.7%) and 11/19 (57.9%), 14/19 (73.7%), 9/19 (47.4%) and 8/19 (42.1%), and 8/19 (42.1%), 4/19 (21.1%) and 0/19 (0%), respectively. The median overall survival from the original breast cancer diagnosis was 88 (range, 11–133), 75 (range, 9–115), and 49 (range, 10–64) months in the HAIC/PVIC, TACE and TAE groups, respectively. Grade I–II and grade III–IV bone marrow suppression was observed in 12/19 (63.2%) and 3/19 (15.8%) patients in the HAIC/PVIC group, respectively, in 17/19 (89.5%) and 5/19 (26.3%) patients in the TACE group, respectively, and in 0/19 (0%) and 0/19 (0%) patients in the TAE group, respectively.

Conclusions: HAIC/PVIC with the same regional chemotherapy regimen of the original systemic treatment is feasible, and can benefit patients with UBCLM, who have progressed on prior systemic therapies.

Keywords: Unresectable breast cancer liver metastases (UBCLM); hepatic arterial infusion chemotherapy/portal vein infusion chemotherapy (HAIC/PVIC); prognosis

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Introduction

Approximately 50% of patients with metastatic breast cancer will have liver involvement at some point during the course of their disease, and 5–12% of patients with metastatic breast cancer will have liver involvement (1-3). In these patients, unresectable breast cancer liver metastasis (UBCLM) is a major cause of mortality, and this is associated with poor prognosis. Breast cancer is the second leading cause of cancer-related death among women in the United States, with an estimated 39,840 deaths from breast cancer in 2010 (4).

The treatments for metastatic disease include cryotherapy, percutaneous ethanol injection, interstitial laser therapy, radiofrequency ablation, and hepatic arterial infusion (HAI) transarterial chemoembolization. These therapies have been well-studied in patients with unresectable liver metastases from colorectal cancer (CRC). However, the efficacy of these treatments in patients with UBCLM remains unclear.

Systemic chemotherapy has been widely used as a postoperative adjuvant therapy for breast cancer, and cyclophosphamidum + epirubicin + 5-fluorouracil (CEA) is one of the most commonly used regimens. However, regardless of the administration of CEA and according to standard guidelines, a significant number of patients developed liver metastases during or after chemotherapy, and most of them had no chance for further surgical resection. The aim of the present study was to compare different treatment modalities, in order to guide patients in the selection of an optimal therapy regimen.

Methods

Between October 2014 and January 2002, 57 patients with UBCLM were randomly divided into three groups (n=19, each group): hepatic arterial infusion chemotherapy/portal vein infusion chemotherapy (HAIC/PVIC) group, transcatheter hepatic arterial chemoembolization (TACE) group, and transcatheter arterial embolization (TAE) group. The clinical protocol was reviewed and approved by the Institutional Review Board of Hubei Cancer Hospital, and all study participants provided a written informed consent prior to the therapy.

All patients were diagnosed with breast cancer liver metastasis (BCLM) by percutaneous liver biopsy, and the pathological characteristics of the liver metastases were comparable with those of the primary breast tumor. However, there were no differences between liver metastasis tumors and primary breast cancer tumors. This study was conducted with approval from the Ethics Committee of Hubei Cancer Hospital. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Inclusion criteria: (I) patients who underwent surgery for breast cancer; (II) patients who received six cycles of systemic chemotherapy with CEA; (III) patients with an Eastern Cooperative Oncology Group performance status of 0 or 1; (IV) patients with a liver function test result of Child-Pugh grade A–B. Exclusion criteria: (I) patients with a total bilirubin concentration of >1.0 mg/dL; (II) patients with a serum creatinine concentration of >1.5 mg/dL; (III) patients with coagulation disorders.

All patients in the HAIC/PVIC group underwent the angiographic placement of two catheters in the hepatic artery and portal vein. The Bard Access Ports (the detailed information is presented below) were inserted into the right gastro-omental artery and right gastro-omental vein to establish regional chemotherapy channels for patients in the HAIC/PVIC group. Each individual in this group was infused using arterial and portal vein pumps, in order to equally deliver the following three drugs in both channels through 24 hours of continuous infusion: 600 mg/m^2 of cyclophosphamide at day 1, 100 mg/m^2 of epirubicin at day 1, and 600 mg/m^2 of 5-fluorouracil at day 1 and 8. This was repeated every 21 days, except in cases of tumor progression (the detailed information on the use of these drugs is presented below), or the occurrence of side effects, such as bone marrow suppression, fulminate hepatitis, or other toxicities greater than grade 3. In the TACE group, the chemotherapy regimens were 600 mg/m^2 of cyclophosphamide, 100 mg/m^2 of epirubicin, and 600 mg/m^2 of 5-fluorouracil, with iodipin embolization. In the TAE group, the patients only received iodipin embolization. The Bard Access Ports were purchased from West Amelia Earhart Drive, Salt Lake City, Utah, USA. The cytotoxic drugs included 5-fluorouracil (Jinyao Amino Acid Co., Ltd., Tianjin, China), adriamycin (ADM; Zhejiang Hisun Pharmaceutical Co., Ltd.) and cyclophosphamide (CPA; Jiangsu Hengrui Medicine Co., Ltd.).

The main observational indicators included the level of serum tumor marker CA153, tumor size and number, liver function, complications and overall survival (OS). Local therapeutic efficacy was evaluated by contrast-enhanced dynamic computed tomography (CT) scanning after two courses of chemotherapy, or in cases of clinical suspicion of

recurrence. Clinical tumor recurrence and response were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0) (5). Toxic effects were assessed during hospitalization and at baseline, according to the National Cancer Institute Common Toxicity Criteria guidelines, version 2.0. Complete blood count (CBC), liver function status, complications including chemotherapy-related diarrhea, and bone marrow stifled were assessed.

Statistical methods

The clinical responses were compared between the three groups using chi-square test. Kaplan-Meier analysis was used to assess the OS, and the significance of the differences in survival curves was determined by log-rank test. OS was defined as a period from the date of chemotherapy to the date of death. P<0.05 was considered statistically significant for all analyses. GraphPad Prism 5 software was used for the statistical analysis.

Results

Characteristics of patients in the three groups

The 57 cases of UBCLM were randomly divided into three groups: HAIC/PVIC group, TACE group and TAE groups. The mean age of patients in each group was 55 (range, 37–66), 52 (range, 39–67) and 51 (range, 38–64) years old, respectively. However, there were no significant differences in the clinicopathological characteristics of patients among these three groups (P>0.05, *Table 1*).

Clinical observational indicators

Bard Access Ports were inserted into the right gastro-omental artery and right gastro-omental vein to establish regional chemotherapy channels for patients in the HAIC/PVIC group. Each patient in the HAIC/PVIC group was infused with the three drugs described above by arterial and portal vein pumps, while the other two groups underwent TACE and TAE. Patients received a median of 6 (range, 3–13) HAIC/PVIC, 5 (range, 4–9) TACE, and 6 (range, 4–8) TAE treatments, and there were 17/19 (89.5%), 11/19 (57.9%), and 4/19 (21.1%) objective responses, respectively.

In the HAIC/PVIC, TACE and TAE groups, tumor size was reduced in 15/19 (78.9%), 9/19 (47.4%), and 2/19 (10.5%) cases, respectively, as determined by CT or magnetic resonance imaging (MRI), disease stabilization was observed in 2/19 (10.5%), 4/19 (21.1%), and 2/19 (10.5%) patients, respectively, and disease progression was observed in 2/19 (10.5%), 6/19 (31.6%), and 15/19 (78.9%) patients, respectively (P<0.05).

Furthermore, CA153 levels decreased in 16 (84.2%) patients in the HAIC/PVIC group, 11 (57.9%) patients in the TACE group, and 6 (31.6%) patients in the TAE group (P<0.05, *Table 2*). The median stable time until hepatic and extrahepatic progression was 43 (range, 5–77), 30 (range, 2–97) and 5 (range, 1–53) months in the HAIC/PVIC, TACE, and TAE groups, respectively, and the survival time after the start of the study was 49 (range, 6–103), 35 (range, 5–96) and 11 (range, 4–27) months, respectively. The 1-, 2- and 3-year survival rates in the HAIC/PVIC, TACE and TAE groups were as follows: 18/19 (94.7%), 14/19 (73.7%) and 11/19 (57.9%), respectively; 14/19 (73.7%), 9/19 (47.4%) and 8/19 (42.1%), respectively; 8/19 (42.1%), 4/19 (21.1%) and 0/19 (0%), respectively.

The median OS from the original breast cancer diagnosis was 88 (range, 11–133), 75 (range, 9–115) and 49 (range, 10–64) months in the HAIC/PVIC, TACE and TAE groups, respectively. No severe complications were observed in these three groups. Gastrointestinal (GI) reaction (mouth ulcers, nausea and emesis) were the most common treatment-related adverse events, while abdominal pain was mainly correlated to embolization. Grade I–II and grade III–IV bone marrow suppression were observed in 12/19 (63.2%) and 3/19 (15.8%) patients, respectively, in the HAI/PVI group, in 17/19 (89.5%) and 5/19 (26.3%) patients, respectively, in the TACE group, respectively, and in 0/19 (0%) and 0/19 (0%) patients, respectively, in the TAE group (*Table 3*).

Discussion

In the present study, the outcomes revealed the following: (I) simultaneous portal vein catheter infusion chemotherapy with HAI could improve the curative effect over HAI alone, due to the consideration of the hepatic artery and portal vein treatment at the same time; (II) breast cancer spreads to the liver, or the liver metastasis becomes serious during failure of systemic chemotherapy. If the specificity of liver blood supply causes the outcome, it was hypothesized that by changing the drug infusion methods by 24-hour continuous infusion with cyclophosphamide, epirubicin and 5-fluorouracil from HAI/portal vein infusion (HAI/PVI), the liver metastasis could be controlled, and better clinical outcomes could thereby be achieved. In the present trial,

Table 1 Clinicopathological characteristics of patients in the three groups

Group	HAIC/PVIC	TACE	TAE
N	19	19	19
Age (years), mean [range]	55 [37–66]	52 [39–67]	51 [38–64]
Menstrual status, N			
Postmenstrual	8	9	6
Premenopausal	11	10	13
ER or PR, N			
Positive	12	13	12
Negative	7	6	7
Her-2, N			
Positive	11	13	11
Negative	8	6	8
ERBB-2, N			
Positive	10	11	9
Negative	9	8	10
Pathological subtype, N			
Infiltrating-ductal	17	2	0
Adenocarcinoma	16	1	2
Simple carcinoma	18	0	1
Stage, N			
I–II	8	11	9
III	11	8	10

HAIC/PVIC, hepatic arterial infusion chemotherapy/portal vein infusion chemotherapy; TACE, transcatheter hepatic arterial chemoembolization; TAE, transcatheter arterial embolization; ER, estrogen receptor; PR, progesterone receptor.

Table 2 Curative effect comparison of three groups

Group	N	Tumor size (CT/MRI), N (%)			CA153 level, N (%)	
		Reduction	Stabilization	Progression	Decrease	Rise/stabilize
HAIC/PVIC	19	15 (78.9)	2 (10.5)	2 (10.5)	16 (84.2)	3 (15.8)
TACE	19	9 (47.4)	4 (21.1)	6 (31.6)	11 (57.9)	8 (42.1)
TAE	19	2 (10.5)	2 (10.5)	15 (78.9)	6 (31.6)	13 (68.4)

CT, computed tomography; MRI, magnetic resonance imaging; HAIC/PVIC, hepatic arterial infusion chemotherapy/portal vein infusion chemotherapy; TACE, transcatheter hepatic arterial chemoembolization; TAE, transcatheter arterial embolization.

patients received a median of six cycles of HAI/PVI, five cycles of TACE and six cycles of TAE, with 89.5%, 57.9% and 21.1% objective responses, respectively. The median stable time until hepatic and extrahepatic progression was 43 months for the HAIC/PVIC group, 30 months for the TACE group, and 5 months for the TAE group. The survival after starting the present observation was 49, 35 and 11 months, respectively. Furthermore, the 1-, 2- and 3-year

Table 3 Complications comparison of three groups

Group	N	Wound infection	Abdominal pain	Hepatic failure	Myelosuppression, N (%)		P value
					Grade I–II	Grade III–IV	
HAIC/PVIC	19	1	3	1	12/19 (63.2)	3/19 (15.8)	<0.05
TACE	19	0	17	5	17/19 (89.5)	5/19 (26.3)	<0.05
TAE	19	0	6	1	0/19 (0)	0/19 (0)	<0.05

HAIC/PVIC, hepatic arterial infusion chemotherapy/portal vein infusion chemotherapy; TACE, transcatheter hepatic arterial chemoembolization; TAE, transcatheter arterial embolization.

survival rates were 94.7%, 73.7% and 42.1% for the HAIC/PVIC group, 73.7%, 47.4% and 21.1% for the TACE group, and 57.9%, 42.1% and 0% for the TAE group. These present results indicate that the HAIC/PVIC group exhibited a better curative effect, when compared to the TACE group. However, the log-rank test revealed that the differences in survival rate were not significant, although the complications were lower. Compared with the TAE group, the other groups all exhibited a dominant status.

In the present study, the hypothesis of treating patients with liver metastases from breast cancer was mainly derived from the observation of one hospitalized patient in our institution. The patient had received six cycles of epirubicin-based chemotherapy after excision of a breast tumor. After five months, the patient presented with unresectable metastasis in the liver. After establishing regional channels in the liver artery and portal vein, chemotherapy was adopted with the same regimens as those received in the systemic chemotherapy. The differences were the use of drug infusion and the change to continuous 5-fluorouracil infusion. The treatment resulted in the reduction in tumor size. This indicates that the change in efficacy may be associated with blood drug concentration, although drug infusion continuity may have also contributed to this effect. Therefore, if the infusion method just needs to be changed, the problem would become simple. Hence, the present experiment was designed. These present results revealed that with the infused chemotherapy using the original systemic chemotherapy regimen from HAI/PVI, the use of systemic drugs remains feasible, and can benefit patients with UBCLM who have progressed on prior systemic therapies. The present study also reveals that the hepatic perfusion characteristics determine the curative effect. Compared with systemic chemotherapy, regional chemotherapy can have the following advantages: The first advantage is the drug concentration in the tumor: The drug concentration in the tumor significantly increases, and improves the efficacy of treatment by acting directly on the tumor tissues. The second advantage is drug effectiveness: Along with the increase in drug concentration in the tumor, the curative effect increases accordingly. Wu *et al.* (6) used drug perfusion by hepatic artery and portal vein channels to improve the regional drug concentration, and concluded that artery and portal vein pump transfusion chemotherapy is efficient for hepatocellular carcinoma treatment.

Breast cancer is one of the most common malignant tumors in women. There are more than one million new cases and 37 thousand deaths each year worldwide, and the incidence of breast cancer is increasing (6). Approximately 30,000 newly diagnosed cases of female breast cancer have been reported in China, with an estimated incidence rate of 42.44 per 100,000 (30.84 per 100,000 in the adjusted rate for China and 28.89/10,000 in the adjusted rate worldwide), accounting for 17.03% of all female cancer cases (7). The main cause of treatment failure is distant metastasis of breast cancer, and the liver is one of the most commonly involved organs. In recent years, regardless of the improvements in the diagnosis and treatment of breast cancer and the curative effects, the long-term prognosis of patients with breast cancer remains poor. Therefore, extensive research efforts have focused on this disease.

Surgical resection is the first choice for patients with BCLM. BCLM refers to focal diffusion, and systemic chemotherapy or endocrine therapy and targeted therapy are the common treatments. However, the efficacy is less than 32%, and the median survival time is 4.5 months. In recent years, the use of chemotherapy regimens, including paclitaxel, has improved the efficacy of treatment. However, the median survival time increased from 9 to 14.7 months (8). In 1997, Pocard summarized the significance of surgical resection to BCLM, and proposed the concept of adjuvant surgery. The authors concluded that adjuvant surgery of hepatic metastases from breast cancer is followed by an uneventful postoperative course, but improves survival

and allows for the discontinuation of chemotherapy in 50% of cases, improving the patient's quality of life (9). However, in patients with a first diagnosis of metastatic breast cancer, liver spread accounts for 15% of cases, and 13% of these cases are only liver metastasis (10). It is possible that the resection of liver metastatic tumors resulted in the improved control of the disease and long-term survival, because the pathway that cancer cells follow to metastasize to the lungs, bones and other parts of the body from the first metastatic liver tumor was blocked. Furthermore, the advances in modern liver surgery have made it possible to ensure the safety of the liver metastasis resection. Published reports have shown that the incidence of complications was 0% in recent decades (10-13). However, in patients with liver metastases from breast cancer, the average survival is merely 10 months (1–47 months) when the liver metastasis is resected. However, the intrahepatic recurrence rate remains high, reaching 12.9–58.3% (10,13-15). In a study that included 52 cases of BCLM, the 36-month follow-up revealed that the survival rates differed according to the lymph node status of the initial breast cancer: 41% for N0–N1 *vs.* 83% for N1b–N2 (16). In patients with poor response to chemotherapy before liver metastasis resection, the recurrence rate remains high. Hence, such operation was thereby not advocated (10).

Research on the comprehensive treatments for liver metastasis was the main focus of the present study. At present, there is extensive evidence-based medicine regarding CRC liver metastasis. This extensive research provides guidelines that surgeons can follow (17,18). However, some of these researches are controversial. Arai *et al.* evaluated the efficacy and adverse events of HAIC using percutaneous catheter placement techniques for liver metastases from CRC. The authors concluded that HAIC did not improve the overall response rate for liver metastasis from CRC (19). Hence, this has become a topic of debate. Furthermore, in order to improve the expectations of patients, scholars have insisted in making great efforts in perform further research. Gofuku *et al.* reported that 14 patients who had liver metastases from breast cancer were treated with TACE or intra-arterial chemotherapy via percutaneously inserted catheters, and revealed that it is possible to achieve a good prognosis when the HAIC effectively controls the liver metastases (20). The survival of patients with UBCLM is a matter of concern, especially in patients with poor liver function. The infusion of large doses of chemotherapy drugs in TACE is associated with high risk. Changing the drug infusion method could improve the chemotherapy drug toxicity tolerance. In the present study, preliminary experiments were performed. Among the five patients with TACE, whose liver function was Child-Pugh grade C, due to the side-effects of large doses of a single drug, three patients had liver failure. Furthermore, in the HAIC/PVIC group, three patients had liver damage, but none of these patients presented with liver failure. The liver function of these patients returned to normal when the tumor reacted to the HAI and the liver metastatic tumor became smaller. Therefore, in the selection of participants, the liver function status of patients should be considered. The preliminary experiments also revealed that the toxicity and side effects were more severe in the TACE group, when compared to those associated with TAE. Some scholars treated patients with the combination of TACE and systemic chemotherapy for liver-only metastases from breast cancer after mastectomy. They concluded that the combined treatment of TACE and systemic chemotherapy may prolong survival in patients with liver metastases from breast cancer (21,22). However, most of these studies were retrospective analyses, and no clinical randomized controlled study, including a large number of samples, could be found.

As for TAE, most studies have focused on HAIC. Ikeda *et al.* treated patients with 30 mg/m^2 of adriamycin on day 1 and 8, and continuously treated patients with 100 mg/m^2 of 5-fluorouracil at level 1, 200 mg/m^2 of 5-fluorouracil at level 2, 300 mg/m^2 of 5-fluorouracil at level 3, and 400 mg/m^2 of 5-fluorouracil at level 4 from day 1 through day 14, every 28 days, through the hepatic artery. At least two cycles were required before the evaluation. A total of 28 patients were entered into this study, and it was revealed that the median duration of response was 5.8 months, and the median survival was 25.3 months. However, catheter-related complications remained an issue (23). Camacho *et al.* treated patients with monthly 24-hour continuous hepatic infusions of 200 mg/m^2 of paclitaxel through an intra-arterial catheter. Three patients (30%) attained partial responses that lasted for 6, 7 and 48 months, while four patients had a stable disease for 5–9 months. Furthermore, one patient underwent liver resection after receiving HAIs of paclitaxel, and remained disease free for 48 months. Eight patients received prior systemic taxane therapy alone or with other cytotoxic agents. It was considered that hepatic intra-arterial therapy with paclitaxel was safe and well-tolerated, and that there was reasonable antitumor activity against breast carcinoma involving the liver. However, previous taxane exposure did not hamper the potential benefit of

this approach. This regimen alone or in combination with targeted therapies deserves further investigation in patients with dominant liver metastases from breast carcinoma (24). Other studies have also provided similar evidences: the use of nonsurgical local therapies, such as HAI or TACE, in patients with metastatic breast cancer with hepatic oligometastasis has been reported (20,23-30). However, none of these studies assessed the effect of perfusion drugs administered from the portal vein.

In conclusion, HAIC/PVIC with regional chemotherapy using the original systemic treatment regimen is feasible, and can benefit patients with UBCLM who have progressed on prior systemic therapies.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.12.59). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The clinical protocol was reviewed and approved by the Institutional Review Board of Hubei Cancer Hospital, and all study participants provided a written informed consent prior to the therapy.

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