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Hepatic Arterial Infusion Chemotherapy Is a Feasible Treatment Option for Breast Cancer with Liver-predominant Metastatic Disease

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Abstract. *Background: Patients with liver metastasis from breast cancer (LMBC) are usually offered systemic therapy. However, for those with progressive liver disease and limited extra-hepatic conditions, local liver management becomes an option. Herein we present our experience with hepatic arterial infusion chemotherapy (HAIC). Patients and Methods: From 1999 to 2018, 42 patients with LMBC, who had progressive liver metastasis after systemic therapy, were treated with HAIC. A catheter was placed angiographically into the hepatic artery and remained there for 5 consecutive days. One cycle of chemotherapy consisted of mitoxantrone, 5-fluorouracil, folinic acid, and cisplatin. This treatment was repeated at monthly intervals. The medical records were reviewed and analyzed for hepatic tumor response, progression-free survival, overall survival and adverse effects. Results: Complete response was observed in two patients (5%), partial response in 18 patients (43%) and stable disease in eight patients (19%). Fourteen patients (33%) had progressive disease after HAIC. The median progression-free survival and overall survival were 8.4 and 19.3 months, respectively. There was no death related to HAIC. The patients with response to the treatment had a significant survival benefit ($p<0.005$). Conclusion: HAIC can be an option for those with progressive liver disease who are heavily pretreated while their extra-hepatic conditions are minimal or stable.*

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Breast cancer is one of the most common types of cancer in the world ranking first in cancer-related incidence and second in death (1). Metastatic breast cancer is thought to be incurable. The common metastatic sites are bone, liver, lung, and brain. Median survival of patients with metastatic breast cancer is around 18-24 months (2, 3). Patients with metastasis may respond transiently to chemotherapy or endocrine therapy, but most of them exhibit progressive disease changes 1-2 years later (4). Metastatic liver disease may cause impairment of liver function and endanger the patient. Treatments for liver metastasis include systemic chemotherapy, endocrine therapy, surgical intervention, radiofrequency ablation, transcatheter arterial chemoembolization, and hepatic arterial infusion chemotherapy (HAIC) (5-9).

A five-day course of celiac artery infusion chemotherapy regimens including mitoxantrone, 5-fluorouracil (5-FU), folinic acid, and cisplatinum was firstly reported by Beger *et al*., who claimed its effectiveness in preventing liver metastasis after pancreaticoduodenectomy for pancreatic cancer (10). These drugs have also been used in treating breast cancer, either for adjuvant or metastatic settings (11, 12). Since the report of Beger *et al*. in 1999, our Institute has performed HAIC with the Beger regimen for patients with heavily pretreated liver metastasis from breast cancer (LMBC) with or without extrahepatic metastasis. We present our results and compare with the reported series.

Patients and Methods

Study design. The local ethics committee (Human Research Committee of Kaohsiung Veterans General Hospital) was informed about the analyses, and approval was waived due to the retrospective nature of the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Patients. From 1999 to 2018, 42 patients diagnosed with LMBC were treated with HAIC. Before that, most of them had received anthracycline-or taxane-based chemotherapy either for early breast cancer or after metastasis. Surgical resection and radiofrequency ablation of liver tumors were performed in seven and nine patients before HAIC, respectively. Trastuzumab or hormonal treatments were maintained with the treatment if the tumor was human epidermal growth factor receptor 2-positive (HER2+) or hormonal receptor-positive. The interval between the last treatments and HAIC were at least 1 month.

All patients were required to have appropriate hematological, serum aminotransferases, bilirubin, and renal function [absolute neutrophil count (ANC) $\geq 1.5\times10^9$/l, hemoglobin≥8 g/dl and platelet count $\geq 100\times10^9$/l, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤5.0× upper limit of normal, bilirubin ≤2 mg/dl, and serum creatinine ≤1.5mg/dl]. Liver metastasis was confirmed with computed tomography (CT) or magnetic resonance imaging (MRI).

HAIC regimen. A temporary catheter was introduced by the radiologist through the left subclavian artery and the tip of the catheter was placed in the proper hepatic artery. The patients received HAIC via an intra-arterial pump (13). Five courses were planned for each patient. One cycle consisted of 10 mg/m^2 mitoxantrone on day 1, 170 mg/m^2 folinic acid directly followed by 600 mg/m^2 5-FU on days 2 to 4, and 60 mg/m^2 cisplatinum on day 5.

Evaluation and follow-up. Abdominal CT scan was the main evaluation tool for the tumor response. Analyses of response to treatment were based on the best response recorded during follow-up. The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) were used for tumor measurement (14). Complete response (CR) was defined as the disappearance of all tumors; partial response (PR) was defined as a decrease of more than 30% in the sum of the longest diameters; progressive disease (PD) was defined as an increase of more than 20% in the sum of the longest diameters or other newly found lesions; stable disease (SD) was defined as neither CR, PR or PD.

Progressive-free survival (PFS) was defined as the time between the first HAIC and the day of diagnosis of PD. Overall survival (OS) was defined as the time between the first HAIC and the day of death.

Toxic analysis. All patients underwent standard clinical and laboratory examination including liver-related parameters at first presentation and during follow up after interventional treatment. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (National Cancer Institute, USA) (15) were used for toxicity assessments of laboratory values and clinical findings.

Statistical analysis. Statistical analysis was performed using SPSS (SPSS 21; IBM Corp., Armonk, NY, USA). Descriptive analysis of patient characteristics and findings was performed with continuous variables displayed as median with standard deviation or range and frequency data displayed as counts. The intergroup differences in categorical variables were analyzed by one-way ANOVA test. Survival (from first diagnosis, first diagnosis of liver metastases, first interventional treatment) was estimated according to the Kaplan–Meier method.

Possible factors influencing survival after first interventional LMBC treatment were included in a univariate Cox model. Multivariate analysis was performed by Cox proportional-hazard regression model. The log-rank test was used for survival comparison. Values of $p<0.05$ were considered statistically significant.

Results

Patient characteristics. A total of 42 patients with LMBC were enrolled on the protocol between February 1999 and March 2018. All of them were evaluable in respect of the treatment efficacy and safety. The median age was 47.5 years (range=22-67 years). Tumors were hormone receptor-positive in 32 patients (76%) and HER2-positive in 12 (29%) (Table I). Eighteen patients (43%) had liver biopsy before HAIC. Postoperative adjuvant systemic therapy for primary breast cancer included anthracycline regimen such as epirubicin and cyclophosphamide (EC) or 5-FU and epirubicin and cyclophosphamide (FEC) for 40 patients (95%), taxane for 39 patients (93%), hormonal therapy for 32 patients (76%) (Table II).

Twenty-one (50%) patients had evidence of limited extrahepatic disease at the time of interventional LMBC treatment (bone metastases only, 11 patients; extrahepatic disease other than bone metastases, 10 patients). The mean number of liver metastases was 5.8 (range=1-25). The diameter of the largest liver lesion ranged from 1-6.3 cm (mean=2.3 cm).

All patients had received at least one line of chemotherapy for metastasis before HAIC (Table II). The median number of treatment lines was three with a range between one and five. Twenty-two (52%) patients had received more than three lines of chemotherapy. Sixteen patients (38%) had two lines of chemotherapy, and four (10%) patients were treated with one line before HAIC. Three patients (7%) were observed to have an elevated ALT level. The median interval from diagnosis of LMBC to presentation for HAIC was 5.5 (range=1-64) months. The Eastern Cooperative Oncology Group performance status was 0 in 39 patients (93%), and 1 in three patients (7%). The therapy agents used following HAIC due to disease progression are shown in Table III.

Treatment response. The median number of sessions of HAIC was 2.5 (range=1-6). Nine (21%) patients received one session, and treatment discontinuation was due to disease progression in four patients, thrombosis of hepatic artery in one and refusal of further HAIC in four. The remaining 33 patients tolerated the first session well. Twelve patients received two sessions, seven patients had three, 13 had four and one patient had six.

Two patients (4%) had CR and 18 patients (43%) had PR. Eight patients (19%) achieved SD and 14 patients (33%) had progressive change after HAIC. There were no significant factors predicting which patients were responders (Table I).

PFS and OS. The median PFS was 8.4 months [range=0.8-78, 95% confidence interval (CI)=10.6-15.3 months]. The

Table I. *Clinical characteristics of 42 patients with metastatic breast cancer.*

Characteristic	Response to HAIC				
	Total	CR, PR	SD	PD	*p*-Value
Number	42	20	8	14	
Age, years					
Median (range)	47.5 (22-67)	46 (31-67)	47.5 (22-51)	50.5 (37-60)	0.154
Original tumor status, n (%)					
T1	5 (11%)	3 (15%)	1 (13%)	1 (7%)	0.450
T2	25 (60%)	12 (60%)	4 (50%)	9 (64%)	
T3	10 (24%)	5 (25%)	3 (37%)	2 (14%)	
T4	2 (5%)	0 (0%)	0 (0%)	2 (14%)	
Original lymph node status, n (%)					
N0	11 (26%)	4 (20%)	3 (37%)	4 (29%)	0.770
N1	16 (38%)	7 (35%)	4 (50%)	5 (35%)	
N2	11 (26%)	6 (30%)	1 (13%)	4 (29%)	
N3	4 (10%)	3 (15%)	0 (0%)	1 (7%)	
Histologic type, n (%)					
Invasive ductal carcinoma	38 (90%)	18 (90%)	8 (100%)	12 (86%)	0.360
Invasive lobular carcinoma	2 (5%)	2 (10%)	0 (0%)	0 (0%)	
Other	2 (5%)	0 (0%)	0 (0%)	2 (14%)	
Hormone receptor status, n (%)					
Positive	32 (76%)	17 (85%)	4 (50%)	11 (79%)	0.290
Negative	10 (24%)	3 (15%)	4 (50%)	3 (21%)	
HER2 status, n (%)					
Positive	12 (29%)	5 (25%)	2 (25%)	5 (35%)	0.110
Negative	30 (71%)	15 (75%)	6 (75%)	9 (64%)	
Extrahepatic metastases, n (%)					
No	21 (50%)	10 (50%)	3 (37%)	8 (57%)	0.140
Yes	21 (50%)	10 (50%)	5 (63%)	6 (43%)	
Time from BC diagnosis to liver metastasis, months					
Median (range)	32.1 (0-99)	34.5 (0-99)	31.1 (0-82)	32.6 (0-90.6)	0.950
Time from liver metastases to first HAIC, months					
Median (range)	5.5 (1-64)	2.9 (1-63)	16.3 (1-63)	9.5 (2-64)	0.060
ALT before HAIC, n (%)					
≤ULN	39 (93%)	18 (90%)	7 (87%)	14 (50%)	0.200
>ULN – 3×ULN	3 (7%)	2 (10%)	1 (13%)	0 (0%)	
Prior lines of chemotherapy, n (%)					
1-2	20 (48%)	12 (60%)	3 (37%)	5 (35%)	0.230
≥3	22 (52%)	8 (40%)	5 (63%)	9 (64%)	
Metastatic liver tumor size, n (%)					
≤3 cm	29 (69%)	13 (65%)	6 (75%)	10 (71%)	0.290
>3 cm	13 (31%)	7 (35%)	2 (25%)	4 (29%)	
Metastatic liver tumor number, n (%)					
≤3	17 (40%)	9 (45%)	2 (25%)	6 (43%)	0.140
>3	25 (60%)	11 (55%)	6 (75%)	8 (57%)	
Metastatic lobe of liver, n (%)					
Right/left	20 (48%)	10 (50%)	3 (37%)	7 (50%)	0.800
Bilateral	22 (52%)	10 (50%)	5 (63%)	7 (50%)	

ALT: Alanine aminotransferase; BC: breast cancer; CR: complete response; HER2: human epidermal growth factor receptor 2; HAIC: hepatic arterial infusion chemotherapy; PD: progressive disease; PR: partial response; SD: stable disease; ULN: upper limit of normal.

median OS after first HAIC was 19.3 months (range=3-112 months, 95% CI=14.7-23.8 months) (Figure 1). The median survival time from the initial diagnosis of breast cancer was 62.3 months and from diagnosis of liver metastasis was 23.8 months. The median OS was significantly longer in the responder group (26.7 *versus* 6.1 months, $p<0.001$; Figure 2). The median PFS was significantly longer in patients who had previously received fewer than three lines of systemic chemotherapy compared to those who received three lines or more (12.1 *versus* 5.6 months, $p=0.002$; Figure 3). The

Table II. *Treatment received by patients with metastatic breast cancer prior to hepatic arterial infusion chemotherapy (HAIC).*

	Treatment						
Before HAIC	FEC	EC	FLC	Taxane	Trastuzumab	Hormonal	Other
Yes	35 (83%)	5 (12%)	2 (5%)	39 (93%)	12 (29%)	32 (76%)	23 (55%)
No	7 (17%)	37 (88%)	40 (95%)	3 (7%)	30 (71%)	10 (24%)	19 (45%)

FEC: 5-Fluorouracil, epirubicin and cyclophosphamide; EC: epirubicin and cyclophosphamide; FLC: 5-fluorouracil, lipo-dox and cyclophosphamide.

median PFS and OS did not significantly differ between the patients with and those without extrahepatic lesions.

Univariate Cox regression regarding PFS, we identified fewer than three lines of prior systemic chemotherapy (p=0.005) as a factor associated with a significantly favorable survival rate. In univariate and multivariate analyses of the OS, response of the liver tumors (p<0.001) was found to be a significant prognostic factor. Other factors, such as age (>45 years), original breast tumor size (>2 cm), original number of lymph nodes involved (>3), hormonal receptor status, HER2 status, presence of extrahepatic disease, size of metastatic liver tumors (>3 cm), number of metastatic liver tumor (>3), and tumor markers (cancer antigen 15-3 >30 U/ml and carcinoembryonic antigen >5 ng/ml) had no significant impact on PFS or OS.

Nine patients were still alive at the time of writing. Six patients had died of lung metastasis, five of brain metastasis, and 22 of liver tumor progression.

Table III. *Treatment received by patients with metastatic breast cancer after hepatic arterial infusion chemotherapy (N=23).*

Agent	Number of patients
Anthracycline	3
Taxane	16
Cisplatin	7
Lipo-dox	3
Vinorelbine	6
Eribulin	2
Lapatinib	1
Capecitabine	12
Avastin	2
Ixempra	4
Everolimus	1
5-Fluorouracil	1

Toxicity. The most common hematological toxicities were neutropenia (11%), anemia (2%), thrombocytopenia (2%) and ALT elevation (10%). Non-hematological toxicities included grade I-II anorexia (21%). Two patients had neutropenic fever, two complained of abdominal pain, and one mentioned diarrhea. No treatment-related death was observed (Table IV).

Table IV. *Toxicity experienced by patients treated with hepatic arterial infusion chemotherapy in this study. There were no grade 4 toxicities.*

	Grade, n (%)	
Toxicity	2	3
Neutropenia	1 (2%)	4 (9%)
Anemia	1 (2%)	1 (2%)
Thrombocytopenia	0	0
Increase ALT/AST	1 (2%)	3 (7%)
Nausea/vomiting	6 (14%)	3 (7%)
Diarrhea	1 (2%)	0
Abdominal pain	2 (5%)	0

ALT: Alanine aminotransferase, AST: aspartate aminotransferase.

Discussion

On account of the fact that most metastatic liver tumors are supplied by the hepatic artery, chemotherapeutic agents can be delivered through HAIC more specifically to malignant cells (16, 17). On the other hand, normal hepatocytes that mostly rely on the portal venous system are thus exposed to less chemotherapeutic agent. Therefore, HAIC provides a higher exposure to chemotherapy of malignant cells with minimized toxicities and the higher drug level may also overcome drug resistance. Indeed, chemoperfusion in cancer with liver metastasis has produced promising results for patients with colorectal cancer (18). However, the benefit of HAIC in patients with liver metastasis of breast cancer is not clear and only a few retrospective analyses have been reported with use of intrahepatic infusion for breast cancer (9, 19-22). Whereas colorectal liver metastasis can be regarded as locoregional spread through portal circulation, other tumor types such as breast cancer with liver metastasis may only be the first site

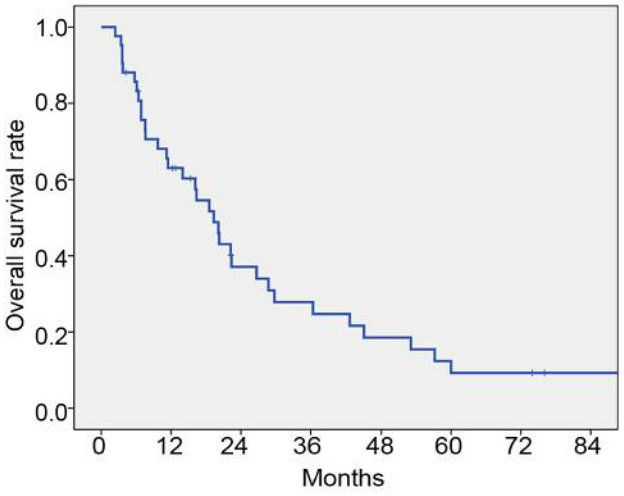

Figure 1. *Kaplan–Meier curve of overall survival for all patients with metastatic breast cancer treated with hepatic arterial infusion chemotherapy. Median overall survival=19.3 (95% confidence interval=14.7-23.8) months.*

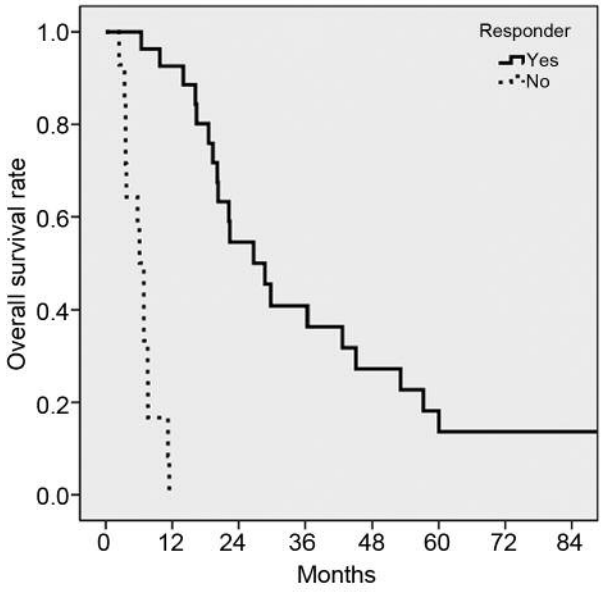

Figure 2. *Kaplan–Meier curves of overall survival for patients with response (complete or partial response, stable disease) and for non-responders (progressive disease) to treatment with hepatic arterial infusion chemotherapy. Median survival: Responders: 26.7 (95% confidence interval=18.3-35.1) months; non-responders: 6.1 (95% confidence interval=4.9-7.3) months; p<0.001. Median survival: Responders: 26.7 (95% confidence interval=18.3-35.1) months; non-responder: 6.1 (95% confidence interval=4.9-7.3) months.*

of distant spread, denoting systemic hematogenous distant micro-metastases elsewhere. Clinically, approximately 50% of patients with breast cancer will develop distant metastases. Liver metastases are present in 15% of patients newly diagnosed with metastatic breast cancer (23, 24), and the liver is the only site of distant disease in one-third of these patients (25). Systemic chemotherapy or hormonal therapy is usually indicated for these patients.

In the present study, we performed HAIC for those patients with liver-predominant metastatic disease when further systemic chemotherapy was not available or deemed ineffective since all the patients had received anthracycline or taxane. The overall response rate was 48%, including two cases of complete response, with an SD rate of 19%. The resulting tumor control rate of 67% was better than the reported series, in which Maes *et al*. (22). and Tsimeridou *et al*. (26). found a response rate of 26.6% and 17.6% with SD rates of 16.7% and 35.3%, respectively (22, 26). Recently, Tewes *et al*. also reported PR in 20% and SD in 38.6% with an HAIC protocol including mitomycin, 5-FU and melphalan (9).

Mitoxantrone is an effective agent for the treatment of advanced breast cancer with mild side-effects, especially with respect to nausea/vomiting, hair loss and cardiotoxicity (27). The literature also confirmed the feasibility of adjuvant therapy in combination with cyclophosphamide and fluorouracil for patients with early breast cancer. For the past decade, mitoxantrone has been used in the treatment of acute myeloid leukemia, hormone-refractory prostate cancer, and multiple sclerosis (28). While its mechanism of action remains incompletely described, it is thought that

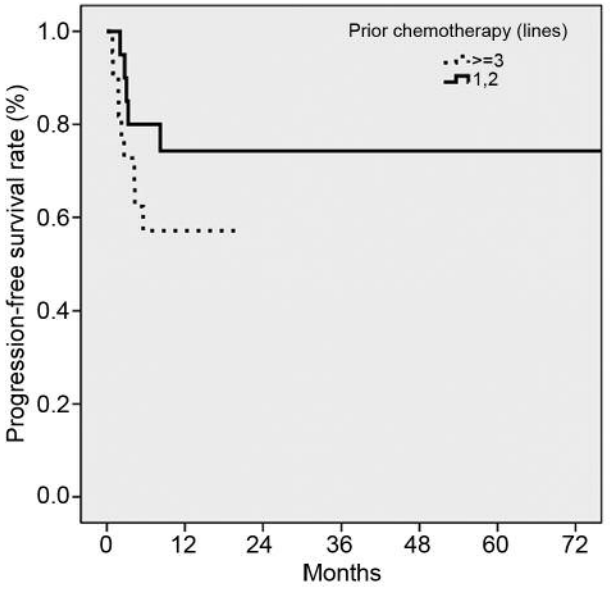

Figure 3. *Kaplan–Meier curves of progression-free survival according to the number of lines of previous chemotherapy before treatment with hepatic arterial infusion chemotherapy. Median survival: Fewer than three lines: 12.1 (95% confidence interval=6.6-17.6) months, more than three lines: 5.6 (95% confidence interval=3.2-7.9) months; p=0.002.*

mitoxantrone intercalates with DNA resulting in DNA strand breaks. In addition, it has been characterized as a DNA type II topoisomerase inhibitor in a bacterial model (29, 30).

In a well designed *in vitro* study, it was demonstrated that mitoxantrone targets ubiquitin specific peptidase 11 (USP11), which is a deubiquitinating enzyme that works in concert with germ-line mutation of breast cancer 2 gene (*BRCA2*) to facilitate DNA homologous recombination by recruiting components of the DNA repair complex (31, 32). In this regard, mitoxantrone may be a good combination component. One of the components in our regimen for HAIC, cisplatin, interacts with DNA, preferentially binding nucleophilic N7 sites on purine bases (33). As a consequence, protein–DNA complexes and DNA–DNA inter-and intra-strand adducts are generated, inducing cytotoxicity. Cisplatin also increases the folate concentration in cancer cells, reinforcing the effect of 5-FU through the formation of an inactive ternary complex (34, 35). Taken together, these preclinical studies showed synergistic chemotherapeutic effect in the regimen used for the present study. In the study of Lekakis *et al*., cisplatin and 5-FU were given with relative safety in the setting of liver dysfunction; many of their patients had liver impairment and were unable to receive other aggressive regimens due to the fact that the liver plays an important role in the metabolism of cytotoxic chemotherapeutics (36).

The choice for the less frequently used mitoxantrone was based on the study of Beger *et al*. (10), revealing tolerable toxicity after intra-arterial admission when combined with 5-FU and cisplatinum. Marjolein *et al*. reported grade 3 and 4 leucopenia rates of 20 and 2%, respectively, using the same protocol for adjuvant intra-arterial chemotherapy and radiotherapy in resectable pancreatic and periampullary cancer (37). The regimen for HAIC in present study was well tolerated and the toxicity profile was more favorable in comparison with mitomycin/5-FU regimens, in which substantial rates of hepatic and hematological adverse effects were found (9).

All patients in our study were heavily pretreated with a median of three previous chemotherapy regimens in treatment for early breast cancer. The median PFS was 8.4 months and median OS from introduction of HAIC was 19.3 months. These data were also better than other reported findings of PFS of 2 to 3 months and OS of 7 months (9, 22). Up to seven lines of systemic chemotherapy before HAIC reported in their studies may be the reason for this difference. Indeed, our analysis also showed that those having received three or more lines of systemic chemotherapy had a shorter PFS. Patients with response to HAIC treatment had a longer OS than those with progressive liver disease, indicating that control of the liver condition played an important role in these patients with liver-predominant metastatic disease.

The retrospective character is the main limitation of this study. The small number of patients was collected over a long period of time. This means that for a prospective randomized trial it may be difficult to recruit appropriate patients. During the study period, a number of advances have also been made in multiple areas of breast cancer treatment. In particular, systemic therapies have improved with the addition of the targeted biological agents such as pertuzumab and trastuzumab emtansine (T-DM1) to the treatment of patients with HER2-positive tumors, and cyclin-dependent kinases 4 and 6 inhibitors to the treatment of patients with hormonal receptor-positive tumors. However, these biological agents may not be financially available for every patient.

Conclusion

Our study proved a viable treatment option for heavily pretreated patients suffering from liver-predominant breast cancer metastasis. The regimen proposed, is safe and may be beneficial in patients whose extra-hepatic conditions are minimal or stable.

Conflicts of Interest

The Authors declare that they have no conflict of interest in regard to this study.

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