The Breast 43 (2019) 113–119

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Hepatic arterial therapy with oxaliplatin and systemic capecitabine for patients with liver metastases from breast cancer

S.C. Lindgaard [a, *], C.M. Brinch [a], B.K. Jensen [a], H.H. Nørgaard [b], K.L. Hermann [b], S. Theile [a], F.O. Larsen [a], B.V. Jensen [a], H. Michelsen [a], K.M. Nelausen [a], V.H. Holm [a], L. Ekblad [c], Peter G. Soerensen [a], D.L. Nielsen [a]

[a] Department of Oncology, Herlev & Gentofte Hospital, University of Copenhagen, Herlev Ringvej 75, DK-2730 Herlev, Denmark
[b] Department of Radiology, Herlev & Gentofte Hospital, University of Copenhagen, Herlev Ringvej 75, DK-2730 Herlev, Denmark
[c] Lund University, Skane University Hospital, Department of Clinical Sciences Lund, Oncology and Pathology, Box 117, SE-221 00 Lund, Sweden

ARTICLE INFO

Article history:
Received 24 April 2018
Received in revised form
26 November 2018
Accepted 3 December 2018
Available online 5 December 2018

Keywords:
Breast neoplasms
Capecitabine
Chemoembolization
Phase II
Oxaliplatin

ABSTRACT

Objectives: Hepatic arterial treatment (HAT) for liver metastases in patients with metastatic breast cancer (MBC) has only been investigated in few studies.
Materials and methods: Two phase II trials were initiated simultaneously to evaluate capecitabine in combination with oxaliplatin in patients with MBC and liver metastases. These two trials are reported together. Continuous capecitabine (1300 mg/m2) was combined with oxaliplatin (85 mg/m2) alternating between systemic treatment and HAT followed by degradable starch microspheres with EmboCept® S every second week. Four patients participated in a pharmacokinetic analysis of oxaliplatin. Each patient had samples taken when receiving oxaliplatin systemically and as HAT with and without EmboCept® S.
Results: Totally, 52 patients received HAT: 14 with liver metastases only and 38 patients with additional limited metastatic disease. The patients had previously received a median of 2 (range 0–6) chemotherapeutic regimens for MBC. The response rate was 42.3% (95% confidence interval (CI) 28.7–56.8%) with 7.7% complete and 34.6% partial responses. Median progression free survival was 10.8 months (95% CI 6.9–14.7 months) and median overall survival 27.6 months (95% CI 20.4–34.8 months). The toxicity was moderate with hand-foot syndrome (15.4%), neuropathy (9.6%), fatigue (9.6%), and abdominal pain (9.6%) being the most common grade 3 adverse events. There was no clear difference between systemic blood concentrations of oxaliplatin when given systemic or as HAT.
Conclusion: HAT oxaliplatin in combination with capecitabine is safe and efficient in patients with MBC. The results are promising with high response rates and a long median progression free and overall survival.

1. Introduction

Breast cancer is the most common cancer in women and the leading cause of female cancer death in Europe [1,2]. About 3–10% of the patients will have distant metastases at the time of diagnosis and the risk of recurrence after treatment for early breast cancer is approximately 20% [3–5]. Despite new treatments metastatic breast cancer (MBC) remains a largely incurable disease. After documentation of distant metastases, the median survival is approximately 2 years with a 5-year mortality of approximately 80% [5–7]. However, MBC is a heterogeneous disease representing different clinical presentations ranging from a solitary metastatic lesion to widespread involvement of multiple organs [6]. Patients with metastatic disease in the visceral organs, especially the liver, are known to have a very poor prognosis with median survival ranging from 5 months in hormone receptor (HR) negative patients to 13 months in HR positive patients [8].

Capecitabine for MBC has been shown to be well tolerated and efficient as both first- and second-line therapy [9,10]. The drug is approved for MBC in combination with docetaxel after failure of prior anthracycline treatment, or as monotherapy in patients resistant to both taxanes and anthracyclines [11].

Oxaliplatin has shown moderate activity in pre-treated patients with MBC [12,13]. The drug has shown efficacy in the treatment of

* Corresponding author. Department of Oncology, Herlev & Gentofte Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.
E-mail address: sidsel.christy.lindgaard@regionh.dk (S.C. Lindgaard).

https://doi.org/10.1016/j.breast.2018.12.002
0960-9776/

anthracycline or taxane refractory MBC in combination with 5-FU and/or vinorelbine, with response rates (RR) of 27–34% [14].

The combination of capecitabine and oxaliplatin is known to have a synergistic effect in patients with colorectal cancer and in breast cancer cell lines [15,16]. Two small studies using a combination of the two drugs have shown promising activity for patients with MBC [12,17]. Furthermore, in a rabbit tumor model, intra-arterial administration of oxaliplatin has shown a significant pharmacokinetic advantage compared with intravenous infusion [18]. Transarterial drug delivery into the liver allows a considerably higher local concentration than when administered systemically. However, there is considerable variation of the first pass hepatic metabolism of chemotherapeutic drugs [22]. Chemotherapy can be applied as hepatic arterial infusion delivered through arterial ports by repetitive hepatic catheterisations, and the intrahepatic drug clearance rate can be reduced by transarterial embolization (TACE). TACE techniques includes infusion with drug eluding beads (DEB-TACE); and infusion of a mixture of chemotherapy and degradable starch microspheres, which temporarily blocks the hepatic arterial blood flow (DSM-TACE) [19].

We report the combined results of two phase II trials of hepatic arterial treatment (HAT) for liver metastases in MBC.

2. Materials and methods

Two trials (MA0918 and MA0919) were initiated simultaneously. Due to difficulty recruiting patients for MA0919 the results of these two trials are reported together. Both trials were approved by the Regional Scientific Ethics Committee (VEK no. H-1-2009-088 and H-1-2009-092, respectively), the Danish Medicine Agency (EudraCT no. 2009-014821-17 and 2009-014863-37, respectively) and informed signed consent was obtained from all patients.

2.1. Patients

All eligible patients were required to have histologically confirmed adenocarcinoma of the breast with metastases in the liver. In MA0919 only liver metastases were allowed, whereas in MA0918 other metastatic sites were allowed if there had been no progression in the extra-hepatic sites within the past 6 months, and if the main cancer burden was intrahepatic. Patients were included if the liver metastases were not eligible for local ablation by radiofrequency ablation (RFA), Stereotactic Body Radiation Therapy (SBRT), or surgery evaluated at a multidisciplinary team (MDT) conference and had <70% of the liver affected. On eligible patients, a CT hepatic arteriography was performed in order to map the hepatic vasculature. Patients were required to be > 18 years, have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) < 2, and have measurable disease according to RECIST 1.1 [20]. All endocrine treatments prior to inclusion were allowed. Previous treatment with a taxane was required. The patients had to have absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l as well as adequate renal and hepatic function. For patients with HER-2 positive tumors, the left ventricular ejection fraction (LVEF) was required to be ≥ 50%.

Patients were excluded if they had a simultaneous malignant disease except from basal cell carcinoma or cervical carcinoma in situ, signs of active cerebral metastases, a severe medical illness or a pre-existing neuropathy ≥ grade 2 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 [21].

2.2. Study design

Patients received oxaliplatin every two weeks alternating between hepatic arterial and systemic administration, except in one case where a permanent catheter was used.

A maximum of twelve series of oxaliplatin was planned. Systemic oxaliplatin was given at a dose of 85 mg/m^2 as an infusion over 30 min. For each HAT, the catheters were inserted percutaneously via the femoral artery in local analgesia and placed in the hepatic artery. Depending on the arterial anatomy the treatment was given in the whole liver in one position of the catheter or split between the right and left liver lobe in two positions. HAT with oxaliplatin was followed by infusion of DSM in a sequential manner in each position of the catheter. For embolization, we used EmboCept® S (450mg/7½ ml, PharmaCept, Berlin, Germany) with a particle mean size of 50 μm. These particles are dissolved by human amylase and cause temporary vascular occlusion with a recanalization time of approximately 1 h [19]. The first treatment for each patient was planned without EmboCept® S.

Since we had no experience with EmboCept® S and the sequential HAT required oxaliplatin infusion rate beyond recommendations, the first six patients were treated at a lower infusion rate.

The first three patients had HAT with 70 mg/m^2 of oxaliplatin during 30 min followed by EmboCept® S to flow stop, maximum 3 ml. This treatment was well tolerated, and dose was increased for the next three patients to 85 mg/m^2 given over 20 min. For the rest of the study population, 85 mg/m^2 oxaliplatin was given over 10 min and EmboCept® S was subsequently given to flow stop, maximum 7.5 ml. Capecitabine was given at a daily dose of 1300 mg/m^2 on a continuous schedule. If treatment continued after the 12 cycles of oxaliplatin, capecitabine 2000 mg/m^2 was given daily for 14 days in 21 days cycles. Patients with HER-2 positive tumors received additional trastuzumab 8 mg/kg on day 1 followed by 6 mg/kg every third week. Patients received routine antiemetic prophylactic treatment and premedication with prednisolone (100 mg), ondansetron (8 mg), pantoprazole (20 mg), atropine (0.5 mg), morphine (10 mg) and occasionally triazolam (0.25 mg).

2.3. Pharmacokinetics

Four patients participated in a pharmacokinetic analysis. They had 2 ml of blood collected at start of the treatment and at the following time points: 0.25, 0.5, 1, 2, 2.5, 3, 4, and 6 h after treatment. Each patient had three different samples taken; one when receiving oxaliplatin systemically, one when receiving oxaliplatin intrahepatically without EmboCept® S and one with EmboCept® S. Plasma levels were determined at the Department of Occupational and Environmental Medicine, Lund University Hospital (Lund, Sweden) by inductively coupled plasma mass spectrometry (ICP-MS; iCAP Q, Thermo Fisher Scientific, Bremen, GmbH) equipped with collision cell with kinetic energy discrimination and helium as collision gas (Supplement file 1).

2.4. Modifications of chemotherapy

Toxicity grading was based on NCI CTCAE version 3.0. Dose adjustments were made as follows: on the day of treatment chemotherapy was delayed if ANC was $<1.5 \times 10^9$/l, platelet count was $<100 \times 10^9$/l or there was any non-hematological toxicity > grade 2. Reductions in dose were performed in patients with febrile neutropenia, grade 4 neutropenia, grade 4 thrombocytopenia, grade 3 thrombocytopenia alongside grade 2 hemorrhage, grade 3 or 4 mucositis, diarrhea or nausea and vomiting despite relevant medical interventions. Additionally, dose reductions of oxaliplatin were carried out according to symptoms, duration and number of times neurotoxicity was reported. Capecitabine was reduced in case of grade 3 hand-foot syndrome or second occurrence of grade 2.

2.5. Baseline and treatment assessments

Complete medical history and physical examination were required before enrolment as well as appropriate laboratory tests and electrocardiogram. Tumor evaluation at baseline was performed with a CT scan or a PET/CT of the chest and abdomen. All patients had a liver biopsy performed within 28 days of inclusion. In MA0918, bone metastases were assessed with Magnetic Resonance Imaging (MRI). Tumor response evaluation was performed with CT-scan after every 4 cycles during treatment and every three months during follow-up. LVEF was measured every three months in patients receiving trastuzumab.

2.6. Statistical methods

The primary endpoint was RR (complete response (CR) + partial response (PR)) in the liver. Secondary endpoints were overall RR, PFS, overall survival (OS) and clinical benefit rate (CBR) (CR + PR + stable disease (SD) for $\geq$ 6 months), number of patients receiving RFA and/or liver resection and toxicity. PFS was calculated as the period from the first treatment to disease progression or death of any cause. Patients who discontinued treatment with capecitabine and started antihormonal therapy were censored the day they initiated endocrine therapy. OS was calculated as the time from the first treatment to death from any cause or until May 1st 2017. Both PFS and OS were estimated with the Kaplan-Meier method [22].

An 1-stage phase 2 design was used to assess the primary endpoint. A RR of 20% was considered promising, whereas a RR of 5% was considered ineffective. With probabilities of a type I error of 0.05 (one-sided test) and a power of 92%, we planned to include 40 eligible patients in each trial (Flemming's Multiple Testing Procedure) [23].

All statistical analyses were conducted using software IBM SPPS Statistics version 22.

3. Results

3.1. Patient characteristics

The intention to treat population was included between October 2009 and September 2016 and comprised a total of 53 patients. One patient received only one systemic treatment but no HAT and was not included in the analyses. Of the remaining patients, 38 had liver and extrahepatic MBC (MA0918) and 14 had only liver metastases (MA0919). Characteristics for all patients included in efficacy analysis are listed in Table 1. The median age was 53.5 years and 90.4% had PS 0. The median number of metastatic sites of was 2 (range 1–4). For patients with extrahepatic MBC, the most common metastatic site was bone (84.2%). At diagnosis, 96.2% were HR positive and 19.2% were HER-2 positive. Three patients changed HER-2 status from HER-2 negative in the primary tumor to HER-2 positive in the metastases. All patients had previously received treatment with taxanes and 75% with anthracyclines. The patients had received a median of 2 (range 0–6) chemotherapeutic regimes for MBC. In general, characteristics for patients in both studies were comparable; however, patients in MA0919 had a shorter time period from diagnosis of metastatic disease to treatment start, with median of 12.0 months compared to 34.1 months for patients in MA0918.

3.2. Treatment

The median number of treatments with oxaliplatin was 12 (range 2–17) and a median of 5 given intrahepatically (range 1–11). One patient had a permanent intrahepatic catheter and therefore received oxaliplatin intrahepatically in all 11 cycles; remaining patients received a maximum of six HAT. Eight patients received more than the planned total of 12 treatments of oxaliplatin. Dose intensity was close to planned with a median dose of systemic oxaliplatin of 79.75 mg/m^2 (range 25.0–91.4 mg/m^2) and intrahepatic oxaliplatin of 82.4 mg/m^2 (range 36.1–88.2 mg/m^2). Intrahepatic oxaliplatin dose was reduced in 33 patients (63%) and systemic oxaliplatin in 34 patients (65%), and 35 patients (67%) had dose delays.

Duration of capecitabine was median 34.7 weeks (range 1.9–143.6 weeks). During the first 12 cycles, the median dose intensity was 81% (20–107%), with dose reductions in 46 patients (88%) and dose delays in 39 patients (75%), respectively.

Following progression, the patients received a median of two antineoplastic regimens (range 0–7), with a median of two chemotherapy regimens (range 0–5) and a median of one antihormonal regimen (range 0–3). The most commonly used regimens were eribulin (n = 28), vinorelbine (n = 17), paclitaxel (n = 12), aromatase inhibitor (n = 20), fulvestrant (n = 19), and trastuzumab emtansine (n = 11). HER-2-directed therapy was given in 13 patients. Four patients received no further anticancer therapy and one patient was still treated with capecitabine without progression at time of analysis.

3.3. Response and survival

RR of the intrahepatic target lesions was 42.3% (95% confidence interval (CI): 28.7–56.8%) with 11.5% CR and 30.8% PR. The overall RR was 42.3% with 7.7% achieving CR and 34.6% PR (Table 2). Two patients subsequently received RFA, one patient was treated with stereotactic radiotherapy, and one had a liver resection without malignant cells in the resected liver. Median PFS was 10.8 months with no difference between the two groups (Table 2). Median OS was 27.6 months for the combined patient population.

Capecitabine was discontinued and followed by antihormonal therapy in 13 patients before progression due to long lasting response (n = 6) or SD (n = 7). Following progression, the patients received a median of two antineoplastic regimens (range 0–7), with a median of two chemotherapy regimens (range 0–5) and a median of one antihormonal regimen (range 0–3). The most commonly used regimens were eribulin (n = 28), vinorelbine (n = 17), paclitaxel (n = 12), aromatase inhibitor (n = 20), fulvestrant (n = 19), and trastuzumab-emtansine (n = 11).

3.4. Toxicity

Toxicity grade 2–4 related to study drug or procedure are shown in Table 3. No patient died due to toxicity. The most common adverse events (AEs) (grade 2–4) were nausea/vomiting (67.3%), sensory neuropathy (65.4%), fatigue (57.7%), and hand foot syndrome (50.0%). Neutropenia (grade 2 and 3) was seen in 28.8%, and thrombocytopenia (grade 2) in 17.3% of the patients. There was no difference in these AEs between the patients being treated intrahepatically or systemically. Abdominal pain (grade 2–3) however, was seen in 34.6% of the patients and only after intrahepatic treatment. Complications to the catheterization occurred in two patients (bleeding grade 1). One patient developed an allergic reaction to EmboCept® S with urticaria responding to treatment with antihistamine.

3.5. Pharmacokinetics

There was no clear difference between the systemic plasma concentrations of oxaliplatin when given intrahepatically or

Table 1
Patient characteristics.

Characteristics		Patients with liver metastases only No. of patients (%) N = 14	Patients with additional metastases outside liver No. of patients (%) N = 38	Combined population No. of patients (%) N = 52
Age, years	Median (range)	52 (36–67)	54.5 (31–72)	53.5 (31–72)
Performance status	0	13 (92.9)	34 (89.5)	47 (90.4)
	1	1 (7.1)	4 (10.5)	5 (9.6)
No. of metastatic sites	Median (range)	1	2 (2–4)	2 (1–4)
	1	14 (100)	0	14 (26.9)
	2	0	29 (76.3)	29 (55.8)
	3	0	8 (21.1)	8 (15.4)
	>3	0	1 (2.6)	1 (1.9)
Type of metastatic site	Liver	14 (100)	38 (100)	52 (100.0)
	Bone	0	32 (84.2)	32 (61.5)
	Lung	0	3 (7.9)	3 (5.8)
	Soft tissue	0	10 (26.3)	10 (19.2)
	Other	0	3 (7.9)	3 (5.8)
Hormone receptor status	Positive	13 (92.9)	37 (97.4)	50 (96.2)
	Negative	1 (7.1)	1 (2.6)	2 (3.8)
HER-2 status, primary	Positive	3 (21.4)	7 (18.4)	10 (19.2)
	Negative	11 (78.6)	31 (81.6)	42 (80.8)
HER-2 status, transformed in metastatic disease	To positive	0	6 (15.8)	6 (11.5)
	To negative	0	0	0
HER-2 status at inclusion	Positive	3 (21.4)	13 (34.2)	16 (30.8)
	Negative	11 (78.6)	25 (65.8)	36 (69.2)
Prior radiotherapy		11 (78.6)	27 (71.1)	38 (73.1)
Prior adjuvant chemotherapy	Cyclophosphamide-based	0	4 (10.5)	4 (7.7)
	Anthracycline-based	7 (50.0)	12 (31.6)	19 (36.5)
	Including a taxane	7 (50.0)	6 (15.8)	13 (25.0)
Prior chemotherapy at	Anthracycline	4 (28.6)	17 (44.7)	21 (40.4)
metastatic disease	Taxane	11 (78.6)	33 (86.8)	44 (84.6)
Prior anthracycline		11 (78.6)	28 (73.7)	39 (75.0)
Prior taxane		14 (100.0)	38 (100.0)	52 (100.0)
No. of chemotherapy regimens for MBC	Median (range)	1.5 (0–2)	2 (1–6)	2 (0–6)
	0	2 (14.3)	0	2 (3.8)
	1	5 (35.7)	10 (26.3)	15 (28.8)
	2	7 (50.0)	15 (39.5)	22 (42.3)
	≥3	0	13 (34.2)	13 (25.0)
Prior endocrine treatment				
Adjuvant	Tamoxifen	8 (57.1)	11 (28.9)	19 (36.5)
	Aromatase inhibitor	3 (21.4)	1 (2.6)	4 (7.7)
	Ovarian suppression	0	1 (2.6)	1 (1.9)
	Other (e.g. combinations)	0	5 (13.2)	5 (9.6)
Metastatic disease, no. of regimens	Median (range)	0 (0–2)	2 (0–4)	1 (0–4)
Prior trastuzumab				
Adjuvant		2 (14.3)	4 (10.5)	6 (11.5)
Metastatic disease		3 (21.4)	10 (26.3)	13 (25.0)
Time from diagnosis to metastatic disease (months)	Median (range)	34.7 (0–106.7)	45.1 (0–188.2)	40.1 (0–188.2)
Time from metastatic disease to treatment start (months)	Median (range)	12.0 (1.4–92.0)	34.0 (8.2–324.2)	29.5 (1.4–324.2)

systemic (Fig. 1). After systemic therapy the mean maximum oxaliplatin plasma concentration (C_{max}) was 2624 μg/L, after intrahepatic oxaliplatin without EmboCept® S it was 3418 μg/L, and after intrahepatic oxaliplatin with EmboCept® S it was 3112 μg/L. Reflecting the different infusion rates of oxaliplatin, C_{max} was reached at 15 min for HAT where oxaliplatin was delivered during 10 min with the first measurement at 15 min and at 30 min for the systemic treatments where oxaliplatin was delivered during 30 min. In two patients oxaliplatin reached a higher concentration when given intrahepatically without EmboCept® S than given with EmboCept® S. For the remaining two patients oxaliplatin concentrations were almost identical. The mean biological half-life was 51 min after intravenous administration, 28 min after HAT without EmboCept® S and 27 min for HAT with EmboCept® S. In Fig. 1, the areas under the curve (AUC_{0-6h}) are as follows: 2473, 2177 and 1978 (μg*hour/L) for intravenous administration, intrahepatic administration without EmboCept® S and intrahepatic administration with EmboCept® S, respectively.

4. Discussion

In these phase II studies we combined therapy with continuous capecitabine with intrahepatic oxaliplatin. Efficacy was determined for 14 patients with unresectable liver metastases only and 38 patients with additional limited extrahepatic metastases. The overall RR was 42.3%, the PFS was 10.8 months and OS was 27.6 months. PFS in the two studies was equally long with 10.8 months for patients with MBC limited to liver and 12.8 months for patient that had liver and extrahepatic MBC. We observed a longer OS for patients with liver metastases only, with 44.7 months compared to 24.0 months. However, this may reflect the difference in the time from diagnosis of metastatic disease to time of treatment start within the study. We saw a high percentage of dose reductions and treatment delays for both oxaliplatin and capecitabine, reflecting the toxicity of the regimen. The balance between toxicity and efficacy is crucial in deciding treatment strategy for patients in an incurable setting such as MBC. A phase III trial is needed to confirm the benefit of HAT for these patients.

Results from a matched control cohort, where patients with

Table 2
Response and survival.

Response rate intrahepatic	Patients with liver metastasis only N = 14		Patients with additional metastasis outside liver N = 38		Combined population N = 52	
	# of pts	Percent (95% CI)	# of pts	Percent (95% CI)	# of pts	Percent (95% CI)
Complete response (CR)	4	28.6 (8.4–58.1)	2	5.3 (0.6–17.8)	6	11.5 (4.4–23.4)
Partial response (PR)	3	21.4 (4.7–50.8)	13	34.2 (19.6–51.4)	16	30.8 (18.7–45.1)
Stable disease (SD)	5	35.7 (12.8–64.9)	21	55.3 (38.3–71.4)	26	50.0 (35.8–64.2)
Progressive disease (PD)	2	14.3 (1.8–42.8)	1	2.6 (0.1–13.8)	3	5.8 (1.2–16.0)
Not evaluable	0	0 (0–23.2)	1	2.6 (0.1–13.8)	1	1.9 (0.1–10.3)
Response rate (CR + PR)	7	50.0 (23.0–77.0)	15	39.5 (24.0–56.6)	22	42.3 (28.7–56.8)
Response rate overall	# of pts	Percent (95% CI)	# of pts	Percent (95% CI)	# of pts	Percent (95% CI)
Complete response (CR)	4	28.6 (8.4–58.1)	0	0 (0–9.3)	4	7.7 (2.1–18.5)
Partial response (PR)	3	21.4 (4.7–50.8)	15	39.5 (24.0–56.6)	18	34.6 (22.0–49.1)
Stable disease (SD)	5	35.7 (12.8–64.9)	21	55.3 (38.3–71.4)	26	50.0 (35.8–64.2)
Progressive disease (PD)	2	14.3 (1.8–42.8)	2	5.3 (0.6–17.8)	4	7.7 (2.1–18.5)
Response rate (CR + PR)	7	50.0 (23.0–77.0)	15	39.5 (24.0–56.6)	22	42.3 (28.7–56.8)
Clinical benefit (CR + PR + SD ≥ 6 months)	10	71.4 (41.9–91.6)	31	81.6 (65.7–92.3)	41	78.9 (65.3–88.9)
	Median (95% CI)		Median (95% CI)		Median (95% CI)	
PFS (months)	10.8* (8.0–13.6)		12.8* (6.9–18.6) *p = 0.819		10.8 (6.9–14.7)	
OS (months)	44.7* (22.0–67.4)		24.0* (17.2–30.8) *p = 0.055		27.6 (20.4–34.8)	

Table 3
Drug and procedure related toxicity.

Toxicity	Grade 2 No. of patients (%)	Grade 3 No. of patients (%)	Grade 4 No. of patients (%)
Hematologic			
Neutropenia	11 (21.2)	4 (7.7)	–
Thrombocytopenia	9 (17.3)	–	–
Non-hematologic			
Nausea/vomiting	32 (61.5)	3 (5.8)	–
Neuropathy (sensory)	29 (55.8)	5 (9.6)	–
Abdominal pain (after intrahepatic treatment)	13 (25.0)[a]	5 (9.6) [a]	–
Hand-foot syndrome	18 (34.6)	8 (15.4)	–
Diarrhea	10 (19.2)	4 (7.7)	–
Fatigue	25 (48.1)	5 (9.6)	–
Mucositis	5 (9.6)	–	–
Infection	4 (7.7)	2 (3.8)	–
Increased amylase	2 (3.8)	1 (1.9)	1 (1.9)
Increased ALAT/ASAT	14 (26.9)	5 (9.6)	–

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.
[a] Related to procedure: 2 patients (1 grade 2 and 1 grade 3).

MBC received systemic capecitabine and oxaliplatin, have been reported from our institution with the following results: RR 28%, median PFS 5.2 months and median OS 12.9 months [24]. These patients (n = 18) had somewhat comparable baseline characteristics to our study cohort with the most common sites for metastases being liver and bone. However, 56% of the patients had an HR^+ tumor and all patients were $HER2^-$, hence this cohort may suffer from a more aggressive disease. Anyhow, compared to this control group our cohort treated with HAT had a markedly increase in both RR, PFS and OS.

Totally, five phase II and one retrospective study have investigated the effect of oxaliplatin in combination with capecitabine or 5-FU in MBC [12,25–29] (Table 4). The studies reported RR from 13% to 50% in patients who were previously exposed to taxanes and/or anthracyclines [28,29]. PFS varied from 3.0 to 6.8 months and OS from 10.0 to 11.9 months. Thus, in the present study, RR was higher and PFS and OS were longer than expected from studies with systemic therapy. However, the patient population in our study may be selected and different from the patient populations in the other studies regarding number of metastatic sites, previous treatment and number of patients with HR positive disease. The effect of intrahepatic chemotherapy in MBC has only been investigated in few studies. More recently, a systematic review reported data from ten studies, of which three were prospective [25]. The studies included from 10 to 208 patients receiving a range of different intrahepatic chemotherapy regimens with or without systemic therapy. RR varied from 7.0 to 73.5%, disease free survival from 2.9 to 17.0 months and OS from 7.3 to 47.0 months. In our study we used EmboCept® S. It was administered subsequently to oxaliplatin. To our knowledge there are no studies indicating whether the administration of EmboCept® S in a mixture with or subsequently to the chemotherapeutic drug has any impact on the outcome.

For MBC patients there are several other available treatment options including CDK4/6 inhibitors, trastuzumab emtansine, and locoregional treatments such as RFA and SBRT [30–32]. A randomized controlled phase III trial is needed for the further evaluation of HAT for these patients.

In vivo, oxaliplatin undergoes rapid biotransformation including multiple active metabolites. Ultrafiltrable platinum (comprising

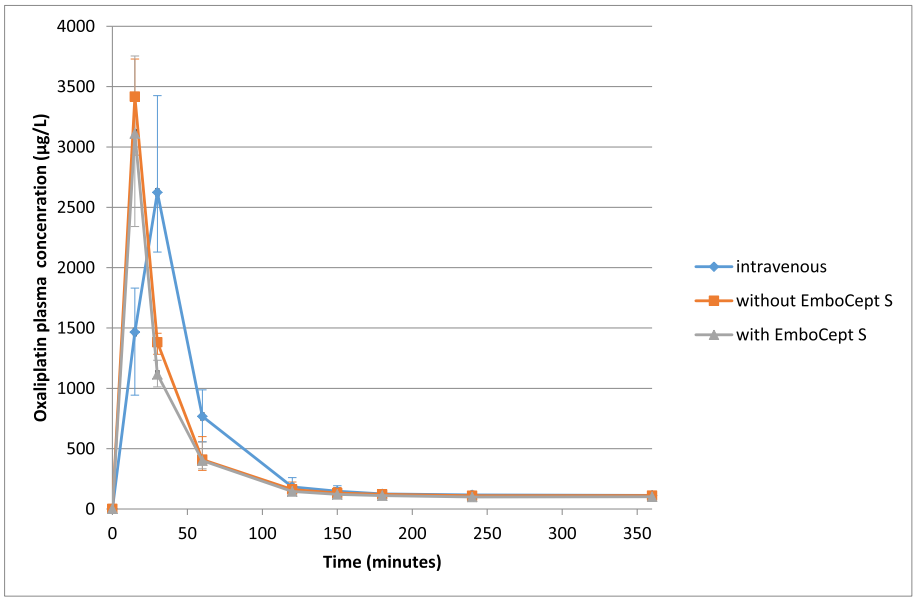

Fig. 1. Pharmacokinetics of oxaliplatin for 4 patients, mean and range.

Table 4
Efficacy of oxaliplatin and capecitabine/5FU.

Reference	Therapy	Phase	Patient characteristics	Number of patients	RR and CBR (%)	Median TTP/PFS (months)	Median OS (months)
Current study	Oxaliplatin HAT/iv + capecitabine	II	ER+ 96%, HER-2+ 25% Prior taxane 100%, anthracycline 75% Prior chemotherapy for MBC: Median 2 (0–6)	52	RR 42.3 (95% CI 28.7–56.8) CBR 78.9 (95% CI 65.3–88.9)	PFS 10.8 (95% CI 6.9–14.7)	27.6 (95% CI 20.4–34.8)
Polyzos et al., 2009	Oxaliplatin iv + capecitabine	II	ER+ 65%, HER-2 NR Prior taxane and anthracycline Prior chemotherapy for MBC: 2-4	28	RR 32 (95% CI 13–51.2) CBR 68	TTP 4.5 (range 2–10)	10 (range 2–18)
Delpeuch et al., 2011	Oxaliplatin iv + capecitabine (n = 23)/gemcitabine (n = 7)	Retro-spective	ER+ 67%, HER-2+ 10% Prior taxane for MBC 73%, prior anthracycline for MBC 50% Prior chemotherapy for MBC: Median 3 (1–6)	30 (15 evaluable)	RR 13	NR	10 (range 1–51)
Zelek et al., 2002	Oxaliplatin iv + 5-FU	II	ER and HER-2 NR Prior taxane, anthracycline Prior chemotherapy for MBC Median 2 (1–6)	64 (60 evaluable)	RR 28 CBR 72	TTP 4.8 (95% CI 3.0–6.5)	11.9 (95% CI 10–13.9)
Sun et al., 2012	Oxaliplatin iv + 5-FU	II	ER+50%, HER-2+ 26% Prior taxane, anthracycline Prior chemotherapy for MBC 41.9%	62 (60 evaluable)	RR 18.3 CBR 31.6[a]	PFS 3 (95% CI 2.5–3.5)	10 (95% CI 6.7 to 13.3)
Li et al., 2015	Oxaliplatin + 5-FU + bevacizumab	II	ER+53%, HER-2- 100% Prior taxane, anthracycline Prior chemotherapy for MBC Median 2 (1–6)	69	RR 50 CBR 56.5[a]	PFS 6.8 (95% CI 5.0–8.5)	10.5 (95% CI 7.9–13.1)

5-FU, 5-fluorouracil; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DFS, disease free interval; ER, estrogen receptor; HER-2, human epidermal growth factor receptor; MBC, metastastic breast cancer; NR, not reported; RR, overall response rate; OS, overall survival; PFS, progression free survival; PR, partial response; SD, stable disease; TTP, time to progression.

[a] CBR = CR + PR + SD ≥ 24 weeks.

non-protein bound drug and biotransformation products in plasma water) is thought to represent all the platinum species with anti-tumor properties in the circulation. Alpha distribution between plasma and tissue is rapid (0.28 h), beta phase is 16 h [33]. Few studies have been conducted to determine the pharmacokinetics of oxaliplatin given intrahepatically. Pharmacokinetics is probably influenced by the degree to which the drug is bound by the embolic material in use. Civallieri et al. examined cisplatin concentration in plasma and in liver tissue after hepatic infusion of a mixture of cisplatin and DSM compared to intrahepatic cisplatin [34]. The addition of DSM resulted in significantly reduced plasma cisplatin in the initial 20 min after infusion, and tissue cisplatin in liver biopsies was increased fourfold. Kern et al. reported the results of 21 patients with colorectal cancer receiving oxaliplatin in combination

with 5-FU intrahepatically [35]. Pharmacokinetic analyses were performed in 18 patients. These analyses suggested reduced systemic availability of the drug when administered intrahepatically as compared to intravenously. We found similar or even higher plasma C_{max} of oxaliplatin when given as HAT. One reason for this finding could be the subsequent administration of EmboCept® S not administered simultaneously with oxaliplatin thus possible not causing embolization before oxaliplatin has passed through the liver to the systemic circulation.

Quality-of-life data was relevant, but not available in this phase II trial. Further studies are necessary to investigate this important issue.

5. Conclusion

In conclusion, HAT with oxaliplatin in combination with capecitabin is both safe and efficient in patients with metastatic breast cancer. There was no clear difference between systemic blood concentrations of oxaliplatin when given as HAT or systemic. The results are promising with both high response rates and a long progression free and median overall survival. Therefore, HAT is a potential loco-regional treatment approach that merits to be evaluated in a randomized phase III trial.

Ethical approval

Both trials were approved by the Regional Scientific Ethics Committee (VEK no. H-1-2009-088 and H-1-2009-092, respectively), the Danish Medicine Agency (EudraCT no. 2009-014821-17 and 2009-014863-37, respectively) and informed signed consent was obtained from all patients.

Conflicts of interest

No conflicts of interest.

Acknowledgements

The study received grant from The Danish Cancer Society.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2018.12.002.

References

[1] Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 Lyon. France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.
[2] ENCR. Breast cancer factsheet. European Network of Cancer Registries; 2014. Available from: http://www.encr.eu/images/docs/factsheets/ENCR_Factsheet_Breast_2014.pdf.
[3] Dieci MV, Arnedos M, Delaloge S, et al. Quantification of residual risk of relapse in breast cancer patients optimally treated. Breast 2013;22(2):S92–5.
[4] Ruiterkamp J, Ernst MF, de Munck L, et al. Improved survival of patients with primary distant metastatic breast cancer in the period of 1995-2008. A nationwide population-based study in The Netherlands. Breast Canc Res Treat 2011;128(2):495–503.
[5] Cardoso F, Harbeck N, Fallowfield L, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(7). vii11–v19.
[6] Nielsen DL, Norgaard H, Vestermark LW, et al. Intrahepatic and systemic therapy with oxaliplatin combined with capecitabine in patients with hepatic metastases from breast cancer. Breast 2012;21(4):556–61.
[7] Bernard-Marty C, Cardoso F, Piccart MJ. Facts and controversies in systemic treatment of metastatic breast cancer. Oncologist 2004;9(6):617–32.
[8] Largillier R, Ferrero JM, Doyen J, et al. Prognostic factors in 1,038 women with metastatic breast cancer. Ann Oncol 2008;19(12):2012–9.
[9] Oshaughnessy JA, Blum J, Moiseyenko V, et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol 2001;12(9):1247–54.
[10] O'Shaughnessy J. Clinical experience of capecitabine in metastatic breast cancer. Eur J Canc 2002;38(2):10–4.
[11] FDA. Highlights of prescribing information xeloda: FDA. 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020896s037lbl.pdf.
[12] Njiaju UO, Tevaarwerk AJ, Kim K, et al. Capecitabine and oxaliplatin in combination as first- or second-line therapy for metastatic breast cancer: a Wisconsin Oncology Network trial. Cancer Chemother Pharmacol 2013;71(3):613–8.
[13] Garufi C, Nistico C, Brienza S, et al. Single-agent oxaliplatin in pretreated advanced breast cancer patients: a phase II study. Ann Oncol 2001;12(2):179–82.
[14] Dean-Colomb W, Esteva FJ. Emerging agents in the treatment of anthracycline- and taxane-refractory metastatic breast cancer. Semin Oncol 2008;35(2 Suppl 2):S31–8. quiz S40.
[15] Raymond E, Buquet-Fagot C, Djelloul S, et al. Antitumor activity of oxaliplatin in combination with 5-fluorouracil and the thymidylate synthase inhibitor AG337 in human colon, breast and ovarian cancers. Anti Cancer Drugs 1997;8(9):876–85.
[16] Cassidy J, Tabernero J, Twelves C, et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. J Clin Oncol 2004;22(11):2084–91.
[17] Polyzos A, Gogas H, Markopoulos C, et al. Salvage chemotherapy with oxaliplatin and capecitabine for breast cancer patients pretreated with anthracyclines and taxanes. Anticancer Res 2009;29(7):2851–6.
[18] Dzodic R, Gomez-Abuin G, Rougier P, et al. Pharmacokinetic advantage of intra-arterial hepatic oxaliplatin administration: comparative results with cisplatin using a rabbit VX2 tumor model. Anti Cancer Drugs 2004;15(6):647–50.
[19] Massmann A, Rodt T, Marquardt S, et al. Transarterial chemoembolization (TACE) for colorectal liver metastases–current status and critical review. Langenbeck's Arch Surg 2015;400(6):641–59.
[20] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Canc 2009;45(2):228–47.
[21] Program CTE. Common Terminology Criteria for adverse events v3.0 (CTCAE): NCI, NIH. 2006. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf.
[22] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958:457–81.
[23] Fleming TR. One-sample multiple testing procedure for phase II clinical trials. Biometrics 1982;38(1):143–51.
[24] Brinch CM, Lindgaard SC, Carlsen D, Soerensen PG and Nielsen DL, A phase II study of capecitabine and oxaliplatin in the treatment of patients with advanced HER-2 negative breast cancer, *J Oncol Res Ther*, JONT-168, https://doi.org/10.29011/2574-710X.000068.
[25] Wang M, Zhang J, Ji S, et al. Transarterial chemoembolisation for breast cancer with liver metastasis: a systematic review. Breast 2017;36:25–30.
[26] Zelek L, Cottu P, Tubiana-Hulin M, et al. Phase II study of oxaliplatin and fluorouracil in taxane- and anthracycline-pretreated breast cancer patients. J Clin Oncol 2002;20(10):2551–8.
[27] Sun S, Wang LP, Zhang J, et al. Phase II study of oxaliplatin plus leucovorin and 5-fluorouracil in heavily pretreated metastatic breast cancer patients. Med Oncol (Northwood, London, England) 2012;29(2):418–24.
[28] Li T, Wang B, Wang Z, et al. Bevacizumab in combination with modified FOLFOX6 in heavily pretreated patients with HER2/neu-negative metastatic breast cancer: a phase II clinical trial. PloS One 2015;10(7), e0133133.
[29] Delpeuch A, Leveque D, Rob L, et al. Off-label use of oxaliplatin in patients with metastatic breast cancer. Anticancer Res 2011;31(5):1765–7.
[30] Krop IE, Lin NU, Blackwell K, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. Ann Oncol 2015;26(1):113–9.
[31] Kumler I, Parner VK, Tuxen MK, et al. Clinical outcome of percutaneous RF-ablation of non-operable patients with liver metastasis from breast cancer. La Radiologia Medica 2015;120(6):536–41.
[32] Messina C, Cattrini C, Buzzatti G, et al. CDK4/6 inhibitors in advanced hormone receptor-positive/HER2-negative breast cancer: a systematic review and meta-analysis of randomized trials. Breast Canc Res Treat 2018;172(1):9–21.
[33] Graham MA, Lockwood GF, Greenslade D, et al. Clinical pharmacokinetics of oxaliplatin: a critical review. Clin Canc Res Offic J Am Assoc Canc Res 2000;6(4):1205–18.
[34] Civalleri D, Esposito M, Fulco RA, et al. Liver and tumor uptake and plasma pharmacokinetic of arterial cisplatin administered with and without starch microspheres in patients with liver metastases. Cancer 1991;68(5):988–94.
[35] Kern W, Beckert B, Lang N, et al. Phase I and pharmacokinetic study of hepatic arterial infusion with oxaliplatin in combination with folinic acid and 5-fluorouracil in patients with hepatic metastases from colorectal cancer. Ann Oncol 2001;12(5):599–603.