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Research Article

A Phase II Study of Capecitabine and Oxaliplatin in the Treatment of Patients with Advanced HER-2 Negative Breast Cancer

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Abstract

Background: There are many treatment options for patients with Metastatic Breast Cancer (MBC) although there is no standard chemotherapy after first line therapy. Capecitabine in combination with oxaliplatin (CapOx) is used in treatment of metastatic colorectal cancer and has shown divergent effect in patients with MBC. This phase II study was initiated to investigate the efficacy and toxicity of CapOx in patients with MBC, pretreated with anthracyclines and taxanes.

Patients and Method: Eighteen patients with HER-2 negative MBC, pretreated with anthracyclines and taxanes, were included. Capecitabine was administered orally continuously at 1300 mg/m2 daily divided on two doses. Oxaliplatin was administered intravenously at 85 mg/m2 every 2 weeks. The study was approved by the Regional Scientific Ethics Committee prior to start of the study.

Results: The best overall response rate was 28% with one CR and four PR's. The Clinical Benefit Rate (CBR; complete response, partial remission and stable disease ≥ 6 months) was 50% and the CBR limit of ≥ 50% was thereby not met and the study was closed. The PFS and OS were 5.2 and 12.9 months, respectively. The treatment was tolerable with no grade 4 toxicity or any drug related deaths. The most common grade 2/3 toxicities were dysesthesia (55%) and sensory neuropathy (55%).

Conclusion: The efficacy of CapOx was not found superior to capecitabine monotherapy. The results from this study do not support the use of CapOx among patients with MBC.

Keywords: Breast Cancer; Capecitabine; Oxaliplatin; Phase II

Abbreviations

CapOx	:	Capecitabine and Oxaliplatin
MBC	:	Metastatic Breast Cancer
TP	:	Thymidine Phosphorylase

Introduction

Breast cancer is the most common cancer affecting women worldwide and represents the leading cause of female cancer death in Europe, estimated to 131.000 deaths in 2012 [1,2]. Most often the disease is considered local at the time of diagnosis and treated with surgery, radiotherapy, chemotherapy and endocrine treatment. Eventually approximately 20% of the patients will experience recurrence either as loco-regional or distant disease [3]. The majority of patients with Metastatic Breast Cancer (MBC) are incurable. Thus, the median Overall Survival (OS) of patients with MBC is approximately 2 years although the survival exceeds five years for about 20% of the patients [4-6]. The treatment include endocrine treatment, chemotherapy and targeted treatment [4]. Most adjuvant chemotherapy regimens include an anthracycline and a taxane [7]. As first line treatment after adjuvant anthracycline, taxane-based chemotherapy is standard care in taxane-naive patients. There are many treatment possibilities for patients with MBC, although there is no standard chemotherapy regimen as second and third line therapy [8]. Patients with MBC are a heterogeneous group. Especially Estrogen Receptor (ER) and HER-2 status have a consequence for the treatment strategy. Patients with ER positive, HER-2 negative MBC would preferable be treated with endocrine therapy unless rapid response is needed, while HER-2 positive

patients should be offered targeted therapy [4].

Capecitabine is an orally administered fluoropyrimidine which is converted to 5-Fluorouracil (5-FU) by three enzymes [9]. One of the enzymes in the cascade is Thymidine Phosphorylase (TP) converting the prodrug to the cytotoxic product 5-FU. The enzyme TP exists in larger amounts in tumor tissue and 5-FU is thereby largely concentrated to these areas [10]. Capecitabine is approved for treatment of colorectal cancer as well as MBC. For the latter, it is approved in combination with docetaxel or as monotherapy after failure of taxane and/or anthracycline based regimens [11].

Oxaliplatin is a diaminocyclohexane platinum. It differs from other platinum derivate and has a low cross-resistance to cisplatin [12,13]. Oxaliplatin is approved for treatment of colon cancer in the adjuvant setting and advanced colorectal cancer in combination with 5-FU [12]. Studies of oxaliplatin monotherapy in patients with breast cancer are sparse. A study including a small number of patients have shown oxaliplatin having moderate efficacy and being well tolerated [14].

Capecitabine and Oxaliplatin (CapOx) have a synergistic antitumor activity in breast and colon cancer cell lines [15]. The combination is an effective treatment of metastatic colorectal cancer [16]. Treatment with CapOx has shown divergent results among patients with MBC [17,18]. This phase II study was designed to investigate the activity and toxicity profile of the combination of oxaliplatin and capecitabine in patients with MBC in a single institution at Herlev & Gentofte Hospital, University of Copenhagen.

Materials and method

Patients

Eligible women were required to have locally advanced or metastatic, histologically or cytologically confirmed breast cancer as well as a HER-2 negative tumor. The patients were also required to have a World Health Organization (WHO) Performance Status (PS) ≤ 2, a life expectancy of ≥ 3 months, at least one measurable lesion according to RECIST 1.1 criteria and documented tumor progression at the time for inclusion [19]. All endocrine treatment prior to inclusion was allowed. Previous adjuvant treatment with taxane and epirubicin or with taxane and cyclophosphamide followed by first line treatment with epirubicin was required. The patients had to have adequate bone marrow function with Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l as well as adequate renal and hepatic function with ASAT/ALAT ≤ 5 x UNL unless the patient had liver metastases.

Patients were excluded from the study if they had a simultaneous malignant disease (except from basal cell carcinoma or cervical carcinoma in situ), pre-existing polyneuropathy > grade 2 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 [20]. Patients having signs of active cerebral metastases, an uncontrolled infection or severe medical disease estimated to counteract with the treatment or hypersensitivity to fluoropyrimidin or any of the active drugs were also excluded from the study. The study was approved by the Regional Scientific Ethics Committee (VEK no. H-4-2013-034), the Danish Medicine Agency (EudraCT no 2012-005329-56) and signed informed consent was obtained from all patients included. The study was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki.

Study Design

Capecitabine was administered orally continuously at 1300 mg/m^2 daily divided on two doses. Oxaliplatin was administered intravenously at 85 mg/m^2 as a 30-minute infusion. Treatment was repeated every 2 weeks. Patients received routine prophylactic antiemetic treatment and premedication with prednisolone (100 mg in total), ondansetron (8 mg) and domperidon as required. Treatment with CapOx was discontinued at tumor progression, intolerable toxicity or patient withdrawal of informed consent. Prophylaxis with Granulocyte-Colony Stimulating Factor (G-CSF) was not recommended.

Modifications of Chemotherapy

Toxicity grading was based on NCI CTCAE version 4.0 [20]. Treatment was delayed if lower limits for ANC and/or platelet count were not met and non-hematological toxicity grade was ≥ 2. The dose was reduced with 25% in patients having febrile neutropenia (temperature ≥ 38.5 and ANC < 1 x 10^9/l), grade 3 thrombocytopenia with simultaneous grade 2 hemorrhage or grade 4 neutropenia or thrombocytopenia. Treatment delay > 2 weeks due to hematological toxicity or grade 3-4 mucositis, diarrhea, nausea or vomiting in spite of relevant medical treatment also led to dose reduction.

The dose was reduced an additional 25% if the side effects were persisting. If bilirubin was increased and persisted at elevated level two weeks after delay of treatment, the treatment was discontinued. If bilirubin decreased to ≤ 2.0 x UNL after delay of treatment, the treatment could restart at a lower dosage level. Neurotoxicity was evaluated, and dose was modified as following. At painless paresthesia persisting > 14 days and painful paresthesia of 7-14 days' duration, dose was reduced to 75% at the first occurrence, 50 % at second occurrence and treatment was discontinued at the third occurrence. In patients experiencing paresthesia with functional impairment lasting 7-14 days, dose was reduced to 50 % at the first occurrence and treatment was discontinued at the second occurrence. Painful paresthesia and paresthesia with functional impairment lasting > 14 days led to

immediate treatment discontinuation.

Baseline and Treatment Assessment

Pre-treatment evaluation included a complete medical history, physical examination, electrocardiogram, appropriate laboratory tests as well as Computed Tomography (CT) scan of chest and abdomen. Magnetic Resonance Imaging (MRI) was performed in selected cases, depending on disease localization. Hematological and biochemical profiles were performed before each cycle (every 2 weeks) and as clinically indicated. Toxicity was assessed at the end of each cycle. Tumor response evaluation with CT scan was scheduled after every four cycles (every 8 weeks) and evaluated according to RECIST 1.1 criteria [19].

Statistics

The primary end point of the study was the Clinical Benefit Rate (CBR; complete response, partial response and stable disease ≥ 6 months). The Progression Free Survival (PFS), Overall Survival (OS) and toxicity were the secondary end points. PFS was calculated as the period from the date of the first treatment to the first observation of disease progression, to death from any cause or the most recent assessment. OS was calculated as the period from the first treatment until death from any cause or until May 2017. PFS and OS were estimated by the Kaplan-Meier method.

The sample size was calculated by Simon's two stage design for phase II trials to allow early discontinuation of the study at a low response rate [21]. The first stage of accrual was planned for 15 patients and the second stage to 43 patients in total. A minimum CBR of >50% was determined (8 out of 15 patients). All statistical analyses were carried out on an intention to treat population. Data was analyzed by using the statistical program SPSS, v22.

Results

Patient Population

A total of 18 patients with MBC were enrolled onto the study between December 2013 and December 2015. (Table 1) depicts patient characteristics. The median age was 57.5 (range 42 to 74 years) and all patients were in PS 0-1. The median time from diagnosis to metastatic disease was 29 months. The patients had a median of three metastatic sites (range one to five) with the most common sites being the liver and bones. The majority of the patients (56 %) had a ER positive tumor. All patients had received taxanes and anthracyclines prior to inclusion. The patients had received a median of one chemotherapy regimens for MBC before inclusion. The overall Response Rate (RR) on prior chemotherapy regimens was 24%.

Characteristics	
Age, years	
Median	57.5
Range	42-74
Performance status	
0	9
1	9
No. of metastatic sites (median, range)	3 (1-5)
1	1
2	4
3	6
>3	7
Type of metastatic site	
Liver	11
Bone	11
Lung and pleura	9
Soft tissue	10
Other	10
Estrogen receptor status	
Positive	10
Negative	8
Radiotherapy	
Yes	12
No	6
Prior neoadjuvant and adjuvant chemotherapy	
CEF[a]	2
EC[b] + taxanes*	9
TC[c]	1
Prior adjuvant hormonal therapy	6
Prior chemotherapy at metastatic disease	
Epirubicine	8
Taxanes	9
Number of chemotherapy regimens for metastatic disease (median, range)	1 (0-2)
0	8
1	3
2	7
≥3 (range)	0
Number of hormonal regimens for metastatic disease (median, range)	0 (0-3)
Time from diagnosis to metastatic disease, months (median, range)	29 (0-135.5)

[a] CEF; cyclophosphamide, epirubicine and 5-fluorouracil. [b] EC: epirubicine and cyclophosphamide. [c] TC: docetaxel and cyclophosphamide. * Two patients received EC + taxanes in neoadjuvant setting.

Table 1: Patient characteristics.

Response, Progression Free and Overall Survival

(Table 2) shows treatment duration and response to capecitabine and oxaliplatin. The patients were treated with a median of 5.5 cycles with CapOx (range from 1 to 17). The best overall response rate was 28% with one CR and four PR's. The clinical benefit rate was 50%. The median PFS and OS were 5.2 and 12.9 months respectively. The reason for end of treatment was PD in 15 patients (83%), toxicity in one patient (6%) and patient's withdrawal of informed consent in two patients (11%). The latter was not related to toxicity.

Characteristic	Total number	Median per patient (range)
Number of cycles with capecitabine	149	5 (1-17)
Number of cycles with oxaliplatin	134	5 (1-16)
Response rate	**No. of patients**	**Percent (95% CI)**
Complete Response (CR)	1	6 (1 -26)
Partial Response (PR)	4	22 (9-45)
Stable Disease (SD)	7	39 (20-61)
Clinical benefit (PR + SD ≥ 6 months)	9	50 (29-71)
Progressive Disease (PD)	6	33 (16-59)
	Months (95% CI)	
Median PFS	5.2 (4.8-5.6)	
Median OS	12.9 (4.1-21.8)	

Table 2: Treatment duration and response to capecitabine and oxaliplatin.

Toxicity

The drug related toxicities are described in (Table 3). No grade 4 or drug related death was reported. The most common grade 2/3 toxicities were dysesthesia (55%), sensory neuropathy (55%) and nausea/vomiting (44%). Neutropenia grade 3 was reported in one and thrombocytopenia grade 2 in two patients. Any form of grade 3 toxicity was reported in eight patients. There were administered a total of 149 and 134 cycles of capecitabine and oxaliplatin, respectively. Delay of treatment was reported in 11% of the cycles with capecitabine and 8% of the cycles with oxaliplatin. The dose of capecitabine and oxaliplatin was reduced in 22 % and 36% of the cycles with CapOx, respectively. After treatment, one patient (6%) had grade 3 and seven patients (37%) grade 2 neuropathies.

Toxicity	Grade 2	Grade 3
	No. of patients (%)	**No. of patients (%)**
Hematologic		
Neutropenia	0 (0)	1 (6)
Trombocytopenia	2 (11)	0 (0)
Non-hematologic		
Neuropathy - dysesthesia	9 (50)	1 (6)
Neuropathy - sensory	10 (56)	0 (0)
Nausea/vomiting	8 (44)	0 (0)
Fatigue	5 (26)	1(6)
Hand-foot reaction	1 (6)	1 (6)
Stomatitis	2 (11)	0 (0)
Infection	1 (6)	0 (0)
Hypokalemia	0 (0)	1 (6)
Paronychion	1 (6)	0 (0)
Increased ALAT/ ASAT	3 (17)	1 (6)
NCI Common Terminology Criteria for Adverse Events version 4.0. There was no grade 4 toxicity.		

Table 3: Drug related toxicity in 18 patients with MBC receiving capecitabine and oxaliplatin.

Discussion

Taxanes and anthracyclines are two of the most potent and broadly effective classes of chemotherapeutic agents in breast cancer. Thus, no standard treatment is available as second or subsequent lines of treatment for patients with MBC who have received these drugs within the course of adjuvant chemotherapy. This study was therefore initiated to investigate a potential new treatment within MBC. The primary end point of our study was the CBR and it amounted 50% (nine of eighteen patients). The results were on the border but did not reach the aim of the study of a CBR limit > 50% (eight of fifteen patients). Therefore, the study was closed. The RR was 28% and the median OS approximately one year. Capecitabine monotherapy is known effective in patients with MBC. In 2006 Ershler made a review of studies using capecitabine as first or second line treatment, in MBC and found a RR of 28% and a median OS of 11 months [22]. A retrospective study by Gilabert et al. from 2011 including patients with HER-2 negative MBC, previously treated with taxanes and anthracyclines found a RR of 29.7% and a median OS of 18 months [23]. Our study found

RR and OS equal to these studies', indicating that the combination therapy with CapOX did not have efficacy superior to this already approved treatment.

Platinum agents have been used in a limited amount within patients with MBC. Studies with cisplatin in chemotherapy naive patients have shown a good RR of approximately 50%. However, in chemotherapy pretreated patients the RR is significantly lower, corresponding to less than 10 %. Carboplatin is known with a more favorable toxicity than cisplatin and has also shown effect in chemotherapy naive patients with MBC with a RR of about 35%, although reduced to less than 10% in chemotherapy pretreated patients [24]. There is one previous study regarding oxaliplatin monotherapy in patients with MBC by Garufi et al. from 2001. This study included 14 patients pretreated with anthracyclines and found a RR of 21 % and a median OS of 12 months. The study showed oxaliplatin having moderate activity in this group of patients and being well tolerated [14]. Several studies have investigated the combination of oxaliplatin and other chemotherapeutic agents among patients with MBC. A RR of 59% and an OS of 18.6 months was found in a phase II study by Guerrero et al. from 2011 including 44 patients with MBC to treatment with vinorelbine and oxaliplatin as first line therapy [25].

Platinum based chemotherapy is also found having a higher RR among patients with triple negative MBC (ER negative, progesterone receptor negative and HER-2 negative) but without significant improvement of OS [26]. There are to our knowledge, two former studies including patients with MBC treated with the combination of capecitabine and oxaliplatin (CapOx). In accordance to our study results, a study by Polyzos et al. from 2009 found a RR of 32% and a median OS of 10 months. There were 28 patients with MBC, pretreated with anthracyclines and taxanes, included [17]. The second study by Njiaju et al. from 2011, including 10 patients treated with CapOx as first or second line of treatment, concluded a RR of 50% and median OS of 19 months [18]. In our study CapOx is used as first, second or third line of treatment. The results are in line with other studies. A study including patients with HER-2 negative MBC showed a RR of 36-61%, 19-39% and 11-36% corresponding to first, second and third line of treatment, respectively. Furthermore, there exist a relationship between treatment response in first line and subsequent lines of treatment. This means that patients having effect of first line chemotherapy have a greater possibility of benefit from subsequent lines of treatment [27].

The survival is known to vary by the subtype of MBC. Our study included exclusively patients with HER-2 negative but both ER positive and ER negative MBC. A retrospective study found a median survival of 27 months, 52 months, 76 - 79 months among patients with ER negative/HER-2 negative, HER-2 positive and ER positive/HER-2 negative, respectively [28]. Site of distant metastasis also vary by the subtype of MBC [29].

Our study found the treatment with capecitabine and oxaliplatin tolerable with no grade 4 toxicity. The most common grade 2/3 toxicities were dysesthesia and sensory neuropathy which were manageable in general. All patients had received previous taxanes. The study by Njiaju et al. closed prematurely due to concern about sensory neuropathy. Eighty-nine percent of the patients experienced neuropathies although none was ≥ 3. The study by Polyzos et al. had fewer grade 3 toxicities than the study by Njiaju et al. and these were primary hematologic.

Conclusion

In conclusion this study demonstrates a doubtful effect of the combination of capecitabine and oxaliplatin in patients with MBC pretreated with anthracyclines and taxanes. The efficacy was not found superior to capecitabine monotherapy. The results from this study do not support the use of CapOx among patients with MBC.

Conflicts of interest: The authors report no conflicts of interest.

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