Pathol. Oncol. Res. (2017) 23:505–511
DOI 10.1007/s12253-016-0129-7

ORIGINAL ARTICLE

Capecitabine in Combination with Docetaxel in First Line in HER2-Negative Metastatic Breast Cancer: an Observational Study

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Received: 26 June 2016 / Accepted: 11 October 2016 / Published online: 22 October 2016

Abstract Due to the limited experience with capecitabine plus docetaxel (XT) combination in the first-line treatment of metastatic breast cancer in Hungary, the main objective of the study was to analyze the effectiveness and tolerability of XT therapy. A prospective, open-label, non-randomized, single-arm, multicenter, observational study was designed. All female patients were eligible whose metastatic breast cancer could be treated with the XT protocol according to the summary of product characteristics of the drugs. The median progression free survival was 9.9 ± 3.0 months. Time to treatment failure was 4.6 ± 5.1 months on average. The overall response rate was 28.9 %, the clinical benefit rate was 73.3 %. The treatment was discontinued in 35.6 % of patients due to disease progression and in 20.0 % due to adverse events (AE). 33 patients with a total of 73 AEs have been reported, and 13 of them had serious adverse events (SAE). The efficacy and the safety profile of XT chemotherapy proven in the study are consistent with the results demonstrated in randomized trials. First-line XT chemotherapy effectively improves the PFS in metastatic breast cancer.

Keywords Capecitabine · Docetaxel · HER2-negative metastatic breast cancer · Toxicity

Introduction

Capecitabine is a derivative of 5′-deoxy-S-fluoro uridine carbonate, which is absorbed from the gastrointestinal tract invariably as a prodrug [1]. To the metabolism of capecitabine into active 5-FU, three activation steps are needed [2]. In the final process step, the thymidine phosphorylase (TP) enzyme plays a key role in creating the active form. The enzyme is present in normal and tumor cells, however, since the expression of TP in most tumor tissues is much higher than in normal tissues, the prodrug's activation and concentration is increased in cancers as compared to that in healthy tissues. This results in relatively selective effect and lower systemic toxicity than the use of intravenous 5-FU [3–5].

In addition to the selective activation of capecitabine in tumors [1, 2], synergy with other anticancer agents such as the taxanes is reported [6]. Docetaxel blocks the

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breakdown of the microtubule system allowing cell division and multiplying, resulting in cell death [8]. It also affects the development of non-cancer cells such as the blood cells, which may cause side effects. According to human cancer xenograft studies, Docetaxel induces TP activity in cancer cells, thereby enhancing the efficacy of capecitabine, thus potentiating the inhibition of tumor growth in colon and breast cancer models [6].

Capecitabine (Xeloda®, Roche) plus docetaxel (XT) therapy is a reasonable choice for the treatment of metastatic breast cancer (MBC) patients who have previously received anthracyclines [7]. The main objective of the XEBRA study was to assess safety and efficacy of XT treatment under real-life circumstances.

Patients and Methods

All the procedures followed were in full accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki declaration. All patients gave informed consent before enrollment into the study authorized by the National and Regional Ethics Committees.

Study Design

XEBRA was a prospective, open-label, non-randomized, single-arm, multicenter, observational study run in Hungary. All female patients whose metastatic breast cancer could be treated with the XT protocol according to the summary of product characteristics of the drugs were eligible.

The data after enrollment were prospectively collected within the frame of routine oncology care of metastatic breast cancer (MBC) patients in 11 Hungarian oncology centers. All assessments and interventions were done in compliance with the international and institutional protocols. The choice of therapy was decided by an oncologist team prior to inclusion.

At the first consultation, demographic data (date of birth, height, weight, performance status, menopausal status), the medical history and the breast cancer-specific data (date of diagnosis, initial stage, immune-histological parameters, surgery, radiotherapy and systemic therapy, disease-free interval after adjuvant therapy [DFI], date of detection and localization of metastases) were collected as extracted from the patient files. Thereafter, all the informations on the therapy with the XT regimen including efficacy and adverse events were collected from the patient files.

Follow-up was continued until the disease progression or the patient's death, withdrawal of the consent, loss of contact with the patient or the closure of the study, depending on the earliest event occurred.

The number of completed capecitabine and docetaxel cycles, date of last dose, reason for treatment discontinuation, dose modifications, response to therapy, date of progression and/or death, impact of treatment on initial symptoms and adverse events (AEs) occurring during therapy were registered.

Inclusion and Exclusion Criteria

The study had no specific inclusion criteria. All the patients could take part in the observational study, who were found suitable to the XT regimen according to the official prescription conditions: HER2-negative MBC patients who have previously received either adjuvant or neoadjuvant chemotherapy with standard regimens containing an anthracycline agent or who have started first-line XT chemotherapy within 3 months prior to enrollment.

The study had no specific exclusion criteria, but the trial excluded patients in whom there was a contraindication to the use of capecitabine included in prescription, such as severe and unexpected reactions to fluoropyrimidine therapy in history, hypersensitivity to fluorouracil, capecitabine, known dihydropyrimidine dehydrogenase (DPD) deficiency, pregnancy and lactation, severe leucopenia, neutropenia, or thrombocytopenia, severe liver injury, severe renal impairment (creatinine clearance below 30 ml / min), treatment with sorivudine or chemical analogues, or if there was a contraindication to any drug in the combination.

Study Endpoints

The primary endpoint was median progression free survival (PFS). PFS was defined as the time between the start of study treatment and the detection of disease progression or death. Secondary endpoints included time to treatment failure (TTF). TTF was defined as the time between the start and stop of all study medication due to any reason including disease progression, toxicity or death of the patient), overall response rate (ORR), clinical benefit rate (CBR), dose modification and mean duration of capecitabine treatment, and its toxicity profile. Serious adverse events (SAEs) were classified according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Statistical Analyses

Data evaluation of demographics, breast tumor-specific medical history, XT chemotherapy, changes due to treatment, secondary endpoints and adverse events was done using descriptive statistics. The analysis of PFS was performed using the Kaplan-Meier method.

Results

Patient- and Tumor-Related Characteristics

Between December 2012 and December 2013, altogether 46 patients were enrolled into the study from 11 of 15 opened centers. Patient- and tumor-related characteristics were analyzed for 45 eligible patients (Table 1), while 1 additional ineligible patient was included in safety analyses only.

The mean ± SD age was 58.6 ± 11.4 years (median: 59.0 years, range 35–83 years). Most patients (n = 35, 79.5 %) were postmenopausal, and 15 (33.3 %) were >65 years old at enrollment.

The mean ± SD age at the initial diagnosis of breast cancer was 53.2 ± 11.2 years (median: 54.0 years, range: 31–81 years) of the population, and 22 patients (48.9 %) had stage 3 disease at that time. Histological diagnosis was invasive ductal carcinoma in 40 patients (88.9 %), invasive lobular cancer in 4 cases (8.9 %), while in 1 (2.2 %), mixed carcinoma was found. Three-quarters (77.8 %) were estrogen receptor (ER)-positive and 60.0 % progesterone receptor (PR)-positive, 9 (20.5 %) were triple negative. Most patients (36, 80.0 %) underwent surgical treatment, and in 34 (75.6 %), radiation therapy was performed. All patients received chemotherapy in the adjuvant and/or neoadjuvant setting (Table 2). In one case no data were available. 29 patients (64.4 %) also received adjuvant endocrine treatment. Half of the patients (48.9 %) had DFI >2 years, and one-third (33.3 %) showed a DFI <1 year.

Table 1 Baseline patient and tumor characteristics

Characteristics		Patients (N = 45)	
		N	%
Stage	0	1	2.2
	1	8	17.8
	2	14	31.1
	3	22	48.9
ER	Negative (≤10 %)	10	22.2
	Positive (>10 %)	35	77.8
PR	Negative (≤10 %)	18	40.0
	Positive (>10 %)	27	60.0
Disease-free/ recurrence-free period	≤1 year	15	33.3
	>1 year and ≤2 years	7	15.6
	>2 years	22	48.9
	No data available	1	2.2
Localization of metastases	Bone	19	42.2
	Lung	18	40.0
	Pleura	13	28.9
	Liver	16	35.6
	Skin	2	4.4
	Other (3 cases: no data available, 8 cases: lymph node)	16	38.1
European Cooperative Oncology Group (ECOG) performance status score	0	26	57.8
	1	16	35.6
	2	2	4.4
	No data available	1	2.2

XT Treatment

In 27 patients (60 %) capecitabine was orally administered at an initial dose of 1250 mg/m^2 twice a day on days 1–14, followed by one week medication-free period. Due to the observational design of the study, no accurate data were available on 18 patients as regards the dose of capecitabine. At the beginning of the study, 80.0 % of the patients (36 patients) received 75 mg/m^2 docetaxel treatment in intravenous infusion once daily on day 1 every 3 weeks, however, for similar reasons, no exact information on the dose of docetaxel was given in 8 cases. Supportive therapy was applied according to institutional protocols.

Efficacy

The best tumor response achieved was complete remission in 1 case, and partial remission (PR) was obtained in 12 cases (26.7 %); stable disease occurred in 20 patients (44.4 %). Disease progression (PD) was reported in 18 cases (40.0 %). Thus, ORR was 28.9 %, while CBR was 73.3 %. According to the patient files, initial tumor-related symptoms improved or disappeared in 16 patients (35.6 %), in 19 cases (42.2 %), however, deteriorated or persisted. There was no such data available in 10 patients (Table 3).

The median PFS was 9.9 ± 3.0 months (95 % CI: 4.1–15.7) (Fig. 1). TTF was 4.6 ± 5.1 months on average (median: 3.00, range: 0–21).

Table 2 Chemotherapeutic regimens applied in the study population in the adjuvant/neoadjuvant setting

Chemotherapeutic regimens	Number of patients n = 45 (%)
AC	3 (6.7)
EC	3 (6.7)
FAC	6 (13.3)
FEC	10 (22.2)
FEC100, then docetaxel	2 (4.4)
ED	4 (8.9)
AC, then paclitaxel	2 (4.4)
TAC	8 (17.8)
Other	7 (15.6)

Table 3 Best tumor response and changes in the initial tumor-related symptoms among the included patients during first-line capecitabine-docetaxel therapy

Response to capecitabine-docetaxel treatment		Patients (N = 45)	
		N	%
Best tumor response	Complete Remission (CR)	1	2.2
	Partial Remission (PR)	12	26.7
	Stable Disease (SD)	20	44.4
	Progressive Disease (PD)	12	26.7
Tumor-related symptoms	Improved	14	31.1
	Ceased	2	4.4
	Persisted	17	37.8
	Deteriorated	2	4.4
	Unknown	10	22.2

Safety

The patients received 6.24 ± 4.80 cycles of capecitabine and 6.20 ± 5.12 cycles of docetaxel on average, but the number of treatment cycles showed high variability (range: 1–26 and 1–25, respectively). The reason for treatment discontinuation in most cases was disease progression or physician's decision by considering the risks of therapy continuation (Table 4). Dose reduction was applied for capecitabine in 20 cases (44.4 %), and docetaxel in 15 cases (33.3 %), due to AE in 14 patients (70.0 %) and 10 patients (63.7 %), respectively.

The most common adverse events were hand foot syndrome (26.1 %), neutropenia (21.7 %), mucositis (8.7 %), and diarrhea (6.5 %). During the study, altogether 73 AEs among 33 patients have been reported, of which 13 (17.8 %) were considered as SAE. Fifteen of the reported AEs (20.6 %) were typical for the XT combination treatment, while 21 (28.8 %) and 26 (35.6 %) events were attributed to capecitabine and docetaxel, respectively. The AEs with an incidence of >5 % was found to be 35 and affected 21 patients (45.7 %), as shown in Table 5. Seventeen AEs (23.3 %) led to cessation of therapy, 9 of which were related to capecitabine, and another 8 to docetaxel. Twenty-four (32.9 %) of the AEs lead to reduction of either capecitabine (n = 14) or docetaxel (n = 10) doses. 52 of the reported AEs (71.2 %) required therapeutic intervention, while 21 (28.8 %) not. Most AEs resolved or improved (59 events, 80.8 %), usually without sequelae (44 events, 60.3 %). Until study completion the outcome of 14 events (19.2 %) remained the same or worsened (Table 6).

SAEs are summarized in Table 7. During the study, a total of 13 SAEs were reported in 8 patients. In 4 patients 1 SAE each, in 3 patients 2 SAEs, and in another patient 3 SAEs were reported. According to the consideration of the investigator, 3 SAEs (23.1 %) were related to the XT combination, 3 other events (23.1 %), were related to capecitabine, and 2 events (15.4 %) to docetaxel therapy. The majority of SAEs (8 events, 61.5 %) resolved without sequelae. One docetaxel treatment-related SAE (neutropenia) had fatal outcome. Three other patients died during the study; none of these deaths was associated with capecitabine or docetaxel treatment.

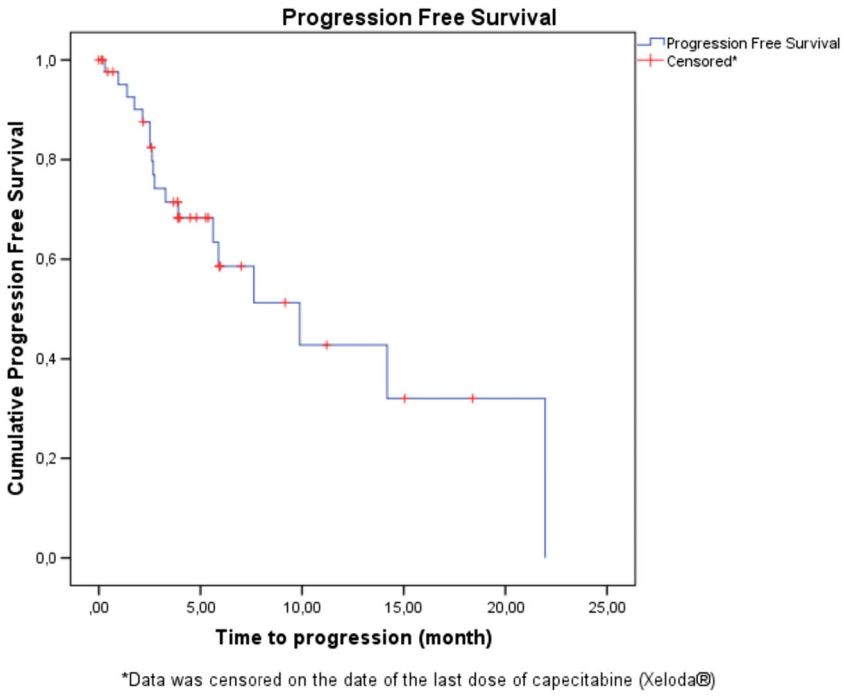

Fig. 1 Kaplan-Meier analysis of progression-free survival in patients treated with first-line XT chemotherapy; median PFS = 9.9 ± 3.0 months (95 % CI: 4.1–15.7)

Table 4 Reasons for treatment (capecitabine vs. docetaxel) discontinuation in the patient population

Reason for treatment discontinuation	Number of patients (%)	
	Capecitabine	Docetaxel
Disease progression	16 (35.6)	12 (26.7)
Death due to other reason (neutropenia)	1 (2.2)	1 (2.2)
Adverse event	9 (20.0)	8 (17.8)
Decision of the physician	12 (26.7)	15 (33.3)
Withdrawal of consent	2 (4.4)	3 (6.7)
The contact with the patient was lost	3 (6.7)	3 (6.7)
Decision of the sponsor	2 (4.4)	1 (2.2)
No data available	0 (0.0)	2 (4.4)

Discussion

The significant anticancer effect of combined XT therapy was first demonstrated in a phase I trial in patients with advanced solid tumors [8]. The study applied a 3-weekly regimen of capecitabine 1250 mg/m^2 twice daily, days 1–14, and docetaxel 75 mg/m^2 on day 1, which was well tolerated, furthermore, in six patients allowed the delivery of ≥23 cycles. This regimen was then evaluated in the large pivotal phase III trial resulting in a time to tumor progression (TTP) of 6.1 months, indicating that second- or third-line XT therapy is highly effective for patients with anthracycline-pretreated MBC. XT combination was significantly superior to docetaxel monotherapy, with significantly superior ORR, TTP, and OS as compared to single-agent docetaxel [9]. The subsequent randomized trials in first-, second- and third-line settings using the same regimen achieved TTP/PFS of 7.9–10 months, median overall survival (OS) of 16.4–28 months and ORR of 38.9–68 % [10–13]. Despite the differences in patient populations, the regimens and the response criteria applied, our data are comparable with these results.

In our study, dose reduction of capecitabine and docetaxel was necessary in 44.4 % and 33.3 % of the patients, respectively. In the pivotal phase III trial [9] the results of patients undergoing early dose reduction, showed unaltered efficacy of the XT combination. Harvey et al. [14] recommended that in patients older than 60 years, a 25 % reduction of the starting dose should be pondered and that a further decrease in the dose of docetaxel to 55–60 mg/m^2 may lead to further benefit regarding the side effects without adverse impact on survival. These data allowed the determination of the most favorable-dose regimen with still high antitumor activity. In phase II clinical trials [12, 15] capecitabine 825 mg/m^2 twice daily, on days 1–14 plus docetaxel 75 mg/m^2 resulted in a median PFS of 5.8–8.5 month, an ORR of 37.4–74 % and a median OS of 15.1–28.6 months. In the study of the Hellenic Oncology Group [16] 950 mg/m^2 capecitabine twice daily was combined with docetaxel 75 mg/m^2. ORR was 53 %, PFS was 11 months and median OS was 35.7 months. Michalaki et al. [17] found a PFS of 8 months, an ORR of 42 % and a median OS of 23 months in patients with MBC, receiving first-line XT therapy of the same regimen. Seidman et al. [18] and Bachelot et al. [19] reported an 8.9–12.4 months PFS, respectively, when applying 1000 mg/m^2 capecitabine twice daily and the usual dose of docetaxel; the median OS was 23.3 months. Bachelot et al. detected an ORR of 64 % and a 2-year OS of 68 % [19]. Yu et al. evaluated that capecitabine in a dose of 1000 mg/m^2 twice a day on days 1–14 combined with docetaxel 35 mg/m^2 on days 1 and 8 yielded a PFS of 8.3 months [20]. The ORR was 12.27 % and the 1-year median OS was 81 %. Gradishar [21] and Blum et al. [22] ascertained that the combination of capecitabine at a reduced dose and 3-weekly or weekly paclitaxel has a high efficacy and a more favorable safety profile.

In our study, neutropenia and hand-foot syndrome (HFS) were the most common adverse events, followed by mucositis and diarrhea. These adverse effects are well known from both the previous studies [7–17] and everyday practice. In the pivotal phase III trial gastrointestinal side effects and HFS occurred more frequently in patients receiving combined chemotherapy [9]. However, myalgia, arthralgia, neutropenic fever and sepsis were more common when docetaxel was used as a single agent. In the studies applying lower doses of capecitabine, HFS and neutropenia were the most common adverse events [17]. At the registered dose, grade 3–4 diarrhea was detected in 18 % of patients [9–11] while in the trials testing a reduced dose of capecitabine [15–17] it was reported in 2–7 % of the cases. At the 1250 mg/m^2 twice a day dose of capecitabine, 18–26 % of the patients developed grade 3 HFS [9–11], whereas

Table 5 Adverse events occurring in >5 % of the cases (n = 46)

Adverse event	Number of patients (%)	Occasion
Neutropenia	10 (21.7)	14
Diarrhea	3 (6.5)	4
Mucositis	4 (8.7)	4
Hand-foot syndrome	12 (26.1)	13

Table 6 The outcome of the adverse events in the ITT population (n = 46)

Outcome of the adverse event	Number of adverse events (%)
Completely recovered	44 (60.3)
Recovered with sequelae	4 (5.5)
Improved	11 (15.1)
Persistent	7 (9.6)
Deteriorated	3 (4.1)
Fatal	4 (5.5)

Table 7 Summary of the serious adverse events reported in the ITT population (n = 46)

Serious adverse event	Number of the patients affected (%)	Number of serious adverse events			
		Total	Treatment-related	Fatal	Treatment-related fatal
Anaemia	1 (2.2)	1	1	0	0
Neutropenia	3 (6.5)	3	3	1	1
Thrombocytopenia	1 (2.2)	1	1	0	0
Heart failure	1 (2.2)	1	0	0	0
Diarrhea	1 (2.2)	1	1	0	0
Disease progression	3 (6.5)	3	0	3	0
Mucositis	1 (2.2)	1	1	0	0
Pneumonia	1 (2.2)	1	0	0	0
Dermatitis	1 (2.2)	1	1	0	0

in the studies examining decreased doses [15–17], 4–13 % only. In general, the safety profile of the XT regimen is better when given at a reduced dose, and side effects are well controlled with either medical interventions or dose reductions.

The aim of our observational study was to collect experiences with the administration of XT chemotherapy in routine practice in Hungarian oncology centres. A limitation of our study was the small size of the population included. Although the study design did not allow the evaluation of the safety, tolerability and efficacy of XT treatment in comparison with a control arm, since these data are well known from large phase II-III clinical studies [9–20], the main goal was the introduction of this new regimen into routine practice. Our findings raise the attention to the importance of appropriate patient selection and toxicity management.

In conclusion, first-line XT therapy effectively improves the PFS of anthracycline-pretreated patients with rapidly progressing HER2-negative breast cancer, visceral metastases and a good physical status. The AEs appearing during treatment are well manageable with modifications in the dose of either capecitabine or docetaxel, significantly improving the tolerability of therapy but without impairing its efficacy.

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