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ORIGINAL ARTICLE

Capecitabine/cisplatin doublet in anthracycline and taxane pretreated and HER-2 negative metastatic breast carcinoma patients

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Summary

Purpose: *To evaluate the activity and toxicity of the combination of capecitabine and cisplatin (CapCisp) in anthracycline- and taxane-pretreated HER-2 negative metastatic breast carcinoma (MBC) female patients.*

Methods: *Patients with HER-2 negative MBC pretreated with anthracycline and taxane and who were then treated with CapCisp combination were retrospectively evaluated. All patients received Cap 1000 mg/m^2 on days 1-14, and Cisp 60 mg/m^2 on day 1, repeated every 3 weeks. In case of disease control without severe toxicity, single agent Cap was continued until progression or unacceptable toxicities after Cisp cessation.*

Results: *Sixty-four MBC patients with median age 43 years (range 20-66) were included the study. Infiltrative ductal carcinoma prevailed (85.9%). Ten percent of the patients had grade I, 42% grade II, and 48.0% grade III tumors. Estrogen receptor (ER) and progesterone receptor (PR) were positive in 48.4 and 51.6% of the patients, respectively. Twenty-eight percent of the patients had triple negative tumors. Almost the entire patient group had this regimen as a third-line treatment. The median combination chemotherapy cycles were 6 (range 2-8). Twenty-seven non-progressive patients continued treatment with single-agent Cap. Median single-agent Cap cycles after the combination chemotherapy were 4 (range 1-38). Disease control rate was 81.3% (complete response 6.3%; partial response 48.4%, stable disease 26.6%, progressive disease 18.8%). Median follow-up time was 10.6 months. Median time to disease progression was 7 months, median overall survival (OS) was 17 months (95% CI, 6.9-16.1) measured from the start of CapCisp chemotherapy. There were no treatment-related deaths. The most frequent grade 3-4 toxicities were neutropenia (8.1%), nausea – vomiting (7.8%) and thrombocytopenia (6.3%).*

Conclusion: *CapCisp doublet has an encouraging antitumor activity with acceptable and manageable toxicity in anthracycline- and taxane-pretreated HER-2 negative metastatic breast carcinoma patients.*

Key words: *breast cancer, capecitabine, cisplatin, HER-2, metastatic*

Introduction

Breast cancer is the most common malignancy in females in the USA, the second most common cause of cancer death in women, and the main cause of mortality in women aged 40 to 59 years [1]. Anthracyclines and taxanes are the most effective drugs used in the treatment of breast cancer. There are a number of studies demonstrating the efficacy of both agents when used in combination or consecutively in neoadjuvant, adjuvant and metastatic settings in breast cancer [2-8]. In addition, there is no standard regimen for MBC patients who were previously treated with anthracycline- and taxane-based chemotherapy.

When determining the treatment schedule

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Table 1. Some characteristic of the patients that may affect the PFS and OS

Characteristics	*N (%)*	*PFS (months)*	*p-value*	*OS (months)*	*p-value*
Total	64 (100)	7		17	-
Age (years)					
< 43	32 (50.0)	6	0.035	13	0.35
≥ 43	32 (50.0)	9		25	
Histology of primary tumor					
IDC	55 (85.9)	7		19	0.32
Other	9 (14.1)	19	0 .16	40 +	
Estrogen receptor					
Positive	33 (48.4)	8	0.71	41	0.68
Negative	31 (51.6)	7		19	
Progesterone receptor					
Positive	41 (64.1)	7	0 .55	31	0.36
Negative	23 (35.9)	9		19	
Triple negative					
Yes	18 (28.1)	7	0.56	14	0.92
No	46 (71.9)	8		17	
Grade (N=52)					
I	5 (9.7)	10	0 .69	53	0.96
II	22 (42.3)	6		25	
III	25 (48.0)	7		12	
Adjuvant HT					
Yes	34 (53.1)	8	0 .55	31	0.36
No	30 (46.9)	6		14	
Metastatic HT					
Yes	30 (46.9)	8	0 .94	14	0.95
No	34 (53.1)	7		31	
Previous 5-FU exposure					
Yes	55 (85.9)	7	0.79	25	0.60
No	9 (14.1)	9		19	
Number of CT lines					
2	2 (3.1)	6	0.030	6	0.35
3	59 (92.2)	8		25	
4	3 (4.7)	3		-	
Number of palliative CT lines					
1	32 (50.0)	7	0.32	25	0.34
2	24 (37.5)	8		19	
3	8 (12.5)	5		13	
Number of metastatic sites					
1	18 (28.1)	8	0.34	42	
2	36 (56.3)	8		12	0.08
≥3	10 (15.6)	6		17	

IDC: invasive ductal carcinoma, HT: hormonotherapy, CT: chemotherapy, PFS: progression free survival, OS: overall survival

for MBC, the treatment algorithm is drawn based on clinical and pathological characteristics. In patients who require chemotherapy, HER-2 status is an important parameter in determining treatment. While monoclonal antibodies which are developed against HER-2 are primarily preferred in HER-2 positive patients, conventional chemotherapy options are used in HER-2 negative patients. There is no standard treatment approach in MBC which was previously treated with anthracyclines and taxanes. Capecitabine is an oral analogue of fluoropyrimidine which is used in the treatment of MBC. Capecitabine, after having proved its efficacy and safety as a single agent in MBC, has started to be used in combination with different agents such as gemcitabine, bevacizumab, and ixabepilone [9-12].

Cisplatin is an alkylating agent widely used in the treatment of solid tumors. It is also used in the treatment of MBC in single or combination regimens. When used as a single agent in patients who have previously received treatment, the response rates are considerably low, however, when used in earlier stages or when combined with other agents, the response rates improve [13-16].

CapCisp was used in head & neck and gastro-

intestinal system tumors and demonstrated to be a safe combination [17-19]. Previously, our group had used the CapCisp combination in MBC following anthracyclines and taxanes and we had reported that this combination was both efficient and, due to its low toxicity profile, a tolerable regimen [20].

In the present study, we aimed to investigate the efficacy and safety of CapCisp combination in patients with MBC, who had previously received anthracycline and taxane chemotherapy, who were HER-2 negative and who had indication for palliative chemotherapy.

Methods

Sixty-four female patients with MBC were included in the study. They all received CapCisp chemotherapy at the Ankara Numune Education and Research Hospital, Medical Oncology Clinic between September 2004 and 2010. All of them had previously received anthracycline and taxane treatment in the neoadjuvant, adjuvant or metastatic settings; their Eastern Cooperative Oncology Group (ECOG) performance status ranged between 0-2 and c-erbB2 was negative immunohistochemically or with FISH. Patients who had received at least two courses of chemotherapy were included in the analysis. Six courses of capecitabine 1000 mg/m^2, days 1-14 and cisplatin 60 mg/m^2, day 1, repeated every 3 weeks were planned. Afterwards, capecitabine was continued as single agent until disease progression or development of unacceptable toxicity. Response Evaluation Criteria in Solid Tumors (RECIST) were used for response evaluation, and National Cancer Institute Common Toxicity Criteria for adverse events were used for toxicity evaluation. Neither G-CSF nor antibiotics were used as primary prophylaxis. Progression free survival (PFS) and OS were calculated from the starting date of the CapCisp protocol.

Statistics

Descriptive analysis was performed for demographic and clinical characteristics of the patients. Student's t-test or Mann-Whitney U test were used for comparison of numeric variables between two groups. X^2 test was used for comparison of ratios between groups. Kaplan-Meier survival curves were generated and compared with log rank test. Statistical analysis was performed with SPSS software version 13.0 (SPSS, Chicago, IL) and statistical significance was set at $p < 0.05$.

Results

Patients

The patient median age was 43 years (range 20-66). While 12 (18.7%) of the patients were metastatic at the time of diagnosis, the remaining (81.3%) had developed metastasis on follow-up. All patients had received anthracycline and taxane therapy as neoadjuvant, adjuvant or palliative therapy. Pre CapCisp adjuvant hormonal therapy was administered to 34 (53.1%) patients, and at least one line of palliative hormonal therapy was administered to 30 (46.9%) patients. The most common pre CapCisp metastastic site was the liver (50.0%), followed by bone (42.2%) and lung (35.9%). The patient demographics are shown in Table 1. Of the patients who showed progression following CapCisp, 32 (50.0%) received a new chemotherapy regimen, 9 (14.1%) received hormonal therapy, while 23 (35.9%) did not receive additional treatment. The most commonly used post CapCisp treatment regimen included protocols with gemcitabine (68.7%).

Treatment

CapCisp was administered as third line treatment to 92.2% of patients with metastatic disease. More than half of the patients (57.8%) completed the planned 6 courses of chemotherapy (median 6, range 2-8). Patients who had a response to treatment with good tolerance and willing to continue treatment, received single-agent capecitabine until disease progression. The median number of courses of single-agent capecitabine was 4 (range 1-38).

Efficacy

The median patient follow-up was 10 months (range 1-70) measured from the starting date of CapCisp. The overall response rate was 54.7%, with complete response in 6.3% of the patients and partial response in 48.4%; stable disease was seen in 26.6% of the patients (disease control 81.3%). Twelve patients (18.7%) showed progression under combination therapy (Table 2). Progression was observed in 56 (87.5%) patients during follow-up. The median time to disease progression

Table 2. Response rates with CapCisp regimen (N=64)

Response	*Patients N*	*%*
Complete response	4	6.3
Partial response	31	48.4
Stable disease	17	26.6
Disease control	52	81.3
Progressive disease	12	18.7

was 7 months (range 1-47; Figure 1), and the median survival 17 months (range 1-70; Figure 2).

Table 3. Toxicities of CapCisp regimen

Toxicities	*N*	*%*
Dose reduction due to toxicity	10	15.7
Treatment discontinuation due to toxicity	4	6.3
Death due to treatment	0	0
Grade 3-4 toxicity	29	31.6
Neutropenia	14	8.1
Anemia	3	4.7
Thrombocytopenia	4	6.3
Nausea-vomiting	5	7.8
Hand-foot syndrome	3	4.7

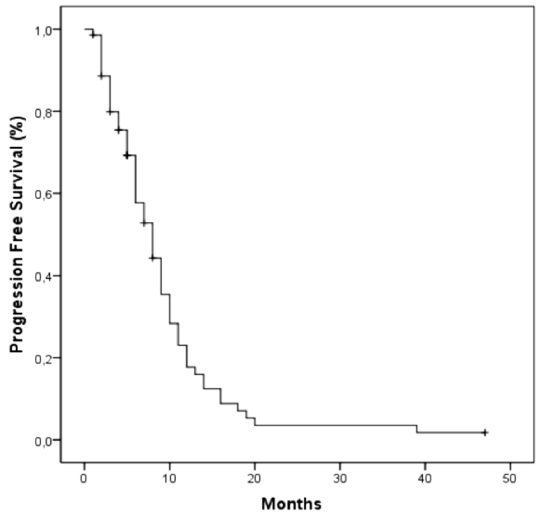

Figure 1. Progression free survival in CapCisp patients (range 1-47 months).

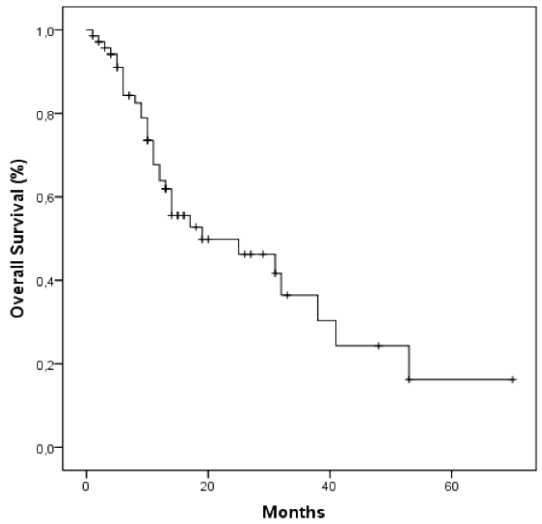

Figure 2. Overall survival in CapCisp patients (range 1-70 months).

Survival

Evaluating the patients in terms of PFS and OS, significant difference in PFS was only observed in the number of chemotherapy lines; however, this difference was possibly due to the fact that more than 90% of the patients received CapCisp therapy as third line. Considering other parameters, PFS was found to be worse in younger patients (p=0.03) and in those with previous intensive treatments (p=0.03), whilst OS did not differ in different subgroups due to the limited number of patients and uneven distribution (Table 1). The triple negative patient rate was 28.1%; there was no significant difference between ER and PR positive groups compared to triple negative group in terms of PFS and OS. Analyzing the cases according to the number of metastatic lesions OS was markedly longer in those with single anatomical region metastasis, yet without statistical significance (Table 1).

Toxicity

No CapCisp therapy-related toxic death was observed. CapCisp was generally well tolerated. Grade 3-4 toxicity was observed in 31.6% of the patients, with myelosuppression being the most common toxicity (19.1%). Nausea, vomiting and hand-foot syndrome were observed at lower rates. Due to grade 3-4 toxicity, dose reduction was required in 15.7%, and treatment discontinuation in 6.3% of the patients (Table 3).

Discussion

Anthracyclines and taxanes are fundamental agents with proven efficacy in every stage of breast cancer. In receptor-negative and hormone-resistant patients who have received anthracycline and taxane-containing therapies, if HER-2 is negative, there is no standard salvage chemotherapy regimen. Various drugs such as gemcitabine, vinorelbine, platinum, capecitabine and PARP inhibitors can be used alone or in combination.

Capecitabine is a tumor-selective fluoropyrimidine converted to 5-flourouracil, preferentially in tumor tissue by thymidine phosphorylase [21]. When used as single agent following anthracycline and taxane treatment, the response rates range between 8-30%, and PFS between 2-6 months. When capecitabine is used in combination with agents such as gemcitabine, vinorelbine, mitomycin, the response rates may increase up to 40% and PFS to 7-8 months (Table 4).

In studies conducted to date on capecitabine as

Table 4. Studies that reported the efficacy of capecitabine and its combination regimens in metastatic breast cancer patients previously treated with anthracyclines and taxanes

Study	*N*	*Treatment arm*	*HER-2*	*RR (%)*	*PFS (months)*	*OS (months)*
Lorusso [22]	38	Cap	Pos/neg	33.0	6.8	11.3
Pajk et al. [23]	47	Cap	NR	8.7	2.8	9.3
Lee et al. [9]	38	Cap	NR	26	4.6	18.1
Kurt et al. [24]	103	Cap	Pos/neg	48.6	6.4	17.1
Wist et al. [25]	48	Cap	NR	33	3.5	9.3
Malmström et al. [26]	34	Cap-Gem	NR	41	4.3	13.7
Benekli et al. [27]	31	Cap-Gem	Pos/neg	10	6	18
Andres et al. [10]	39	Cap-Gem	Pos/neg	48.7	5	10
Maisano et al. [28]	55	Cap-Mit	NR	38	NR	NR
Massacesi et al. [29]	53	Cap-Mit	Pos/neg	37.2	8.1	17.4
Jones et al. [30]	40	Cap-Vin	NR	20	3.4	11.3
Fan et al. [31]	72	Cap-Vin	Pos/neg	45.8	7.7	26.1
Estevez et al. [32]	41	Cap-Vin	NR	49	7.6	27.2
Polyzos et al. [33]	28	Cap-Oxa	NR	32	4.5	10
Oksuzoglu et al. [20]	33	Cap-Cisp	Pos/neg	51.5	6.3	11.5
Current study	64	Cap-Cisp	Neg	54.7	7	17

NR: Not reported, RR: response rate, Cap: capecitabine, Gem: gemcitabine, Mit: mitomycin, Vin: vinorelbine, Oxa: oxaliplatin, Cisp: cisplatin, PFS: progression free survival, OS: overall survival, RR: complete plus partial response

single agent or in combination, all patients were included regardless of HER-2 status. However, HER-2 positive breast cancer is a different entity due to both its clinical course and treatment algorithm and anti-HER-2 therapies comprise the basis of its therapeutic approach. No specific treatment exists for HER-2 negative patients following anthracycline and taxane chemotherapy.

In the present study, we administered the CapCisp chemotherapy protocol to HER-2 negative patients who had previously received both anthracycline and taxane in neoadjuvant, adjuvant or metastatic setting. Of the patients who received capecitabine combination therapy in our study, 50.0% received it as second line treatment for MBC and nearly 50% had received at least one line of palliative hormonal therapy prior to CapCisp; however, 54.7% of the patients achieved complete and partial response and 81.3% disease control, with a response as good as in protocols with gemcitabine, vinorelbine, and mitomycin. We were able to achieve similar results only in HER-2 negative patients when compared with the response rates achieved previously by Oksuzoglu et al. in their CapCisp study on 33 HER-2 positive/negative patients. In terms of survival, CapCisp achieved better survival results with 7 months PFS and 17 months OS. A possible reason for this improvement in survival could be attributed to the exclusion of HER-2 positive patients from the protocol.

Triple negative breast cancers comprise 10-20% of breast cancers and have a poorer prognosis when compared to other cancer types. This poor prognosis is associated with aggressive course of the tumor, increased risk of distant metastasis, and the unavailability of anti-HER-2 and anti-hormone receptor therapy. Once triple negative breast cancers become metastatic, the expected average survival is nearly 13 months [34]. In our study, 28% of the patients were triple negative and their PFS and OS were similar compared to our receptor-positive patients (7 vs 8 months, and 14 vs 17 months, respectively). However, the small number of patients should be taken into consideration. Future studies on triple negative patients alone with larger number of patients may enlight more this topic.

CapCisp combination therapy was generally well tolerated, demonstrating a predictable safety profile. While no toxic deaths were observed, dose reduction or treatment discontinuation developed at a rate of 22%, and grade 3-4 myelotoxicity at a rate of 19.1%. Despite extended use of capecitabine, grade 3-4 hand-foot syndrome was observed only at a rate of 4.7%.

In conclusion, CapCisp combination therapy, with its acceptable toxicity profile, can be used as an effective alternative treatment following anthracycline and taxane in HER-2 negative metastatic breast cancer. Additionally, although CapCisp combination therapy appears to be also effective in triple negative patients, studies involving larger number of patients are needed.

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