

Capecitabine and Oral Cyclophosphamide Combination in Taxane/Anthracycline Resistant Metastatic Breast Cancer

Ahmet OZET, Dogan UNCU, Okan KUZHAN, Seref KOMURCU, Mustafa OZTURK,
Fikret ARPACI, Bekir OZTURK

Gulhane Military Medical Academy, Faculty of Medicine, Department of Medical Oncology, Ankara, TURKEY

ABSTRACT

No combination chemotherapy has been shown yet to be more effective in metastatic breast cancer (MBC) patients who did not either respond to taxanes and anthracyclines or recurred thereafter. We aimed to report in short term the effect and toxicity results of capecitabine and oral cyclophosphamide combination in MBC patients with anthracyclin and taxane resistance.

Between January and September 2007, totally 11 patients were enrolled. All of them had received anthracyclines and taxanes previously either in metastatic or adjuvant setting. They were given capecitabine (1000 mg/m² bid) and oral cyclophosphamide (30 mg/m² tid) on days 1 to 14 every 3 weeks.

Median age of patients was 48 years. The median number of previous chemotherapy lines given was 3. Seven patients had received trastuzumab previously, either as monotherapy or as part of combination chemotherapy. Seven had received capecitabine monotherapy before. Median follow-up was 5 months. The patients received a median of 8 cycles chemotherapy. In 4 patients (36.4%) partial response was obtained. Five patients (45.5%) remained stable, and 2 (18.1%) progressed. Median duration of response was 5 months. At the analysis time, 2 patients were dead. Totally 2 patients (18.1%) had grade 2 leucopenia, 2 (18.1%) had grade 2 hand-foot syndrome, 1 (9.1%) had grade 3 hand-foot syndrome.

Capecitabine and oral cyclophosphamide combination is a promising and well tolerated regimen in patients who previously had received taxanes and anthracyclines and in patients with cerbB2 positive tumors who received trastuzumab previously.

Keywords: Breast neoplasms, Cyclophosphamide, Capecitabine

ÖZET

Antrasiklin ve Taksan Rezistan Metastatik Meme Kanseri Hastalarda Kapesitabin ve Oral Siklofosamid Kombinasyonu

Taksan ve antrasiklinlere yanıt vermeyen veya bu tedaviler sonrasında tekrarlayan metastatik meme kanserli hastalarda daha etkili olduğu gösterilen bir kombinasyon kemoterapisi bulunmamaktadır. Taksan ve antrasiklin rezistan metastatik meme kanserli hastalarda kapesitabin ve oral siklofosamid kombinasyonunun kısa dönemde etkinliği ve toksisitesini bildirmeyi amaçladık.

Ocak ve Eylül 2007 tarihleri arasında toplam 11 hasta çalışmaya alındı. Hastaların hepsi ya adjuvant ya da metastatik dönemde taksan ve antrasiklin tedavisi almışlardı. Hastalara 3 haftada bir 1-14 günler arasında kapesitabin (1000 mg/m² günde 2 defa) ve oral siklofosamid (30 mg/m² günde 3 defa) verildi.

Hastaların ortanca yaşı 48 idi. Önceden aldıkları ortanca kemoterapi rejimi sayısı 3 idi. Yedi hasta ya tek başına ya da kombinasyon kemoterapisi parçası olarak trastuzumab tedavisi almıştı. Yedi hasta önceden kapesitabin monoterapisi almıştı. Ortanca takip süresi 5 ay idi. Hastalar ortanca 8 kür kemoterapi aldı. Dört (%36.4) hastada parsiyel yanıt alındı. Beş (%45.5) hasta stabil kaldı, 2 (%18.1) hastada progresyon gözlemlendi. Ortanca yanıt süresi 5 ay idi. Değerlendirme anında 2 hasta ölmüştü. Toplam olarak 2 (%18.1) hastada grad 2 lökopeni, 2 (%18.1) hastada grad 2 el-ayak sendromu ve 1 (%9.1) hastada grad 3 el-ayak sendromu gelişti.

Kapesitabin ve oral siklofosfamid kombinasyonu önceden taksan, antrasiklin ve cerbB2 pozitif tümörler için trastuzumab tedavisi almış hastalarda iyi tolere edilen ve ümit verici bir rejimdir.

Anahtar Kelimeler: Meme kanseri, Siklofosfamid, Kapesitabin

INTRODUCTION

Metastatic breast cancer (MBC) is an incurable disease. Palliation of symptoms, maintenance of quality of life and tolerability of treatment are particularly important for patients. The most commonly used chemotherapeutic regimens in the treatment of MBC include anthracyclines and taxanes, either in sequence or in combination.¹ An increasing number of patients receive an anthracycline–taxane combination as adjuvant therapy, requiring the development of new combinations for the treatment of metastatic disease. No monotherapy or combination chemotherapy has been shown yet to be more effective in metastatic breast cancer patients who did not either respond to taxanes and anthracyclines or recurred thereafter.

Both cyclophosphamide and capecitabine have some efficacy in breast cancer. Cyclophosphamide is typically used as a component of combination regimens, such as CAF (cyclophosphamide, adriamycin, 5-fluorouracil) or TAC (docetaxel, adriamycin, cyclophosphamide). The oral fluoropyrimidine capecitabine, generates 5-fluorouracil preferentially at the tumor site through exploitation of the significantly higher concentration of thymidine phosphorylase in tumor versus normal tissue.² Capecitabine monotherapy has demonstrated consistently high activity and excellent tolerability in anthracycline- and/or taxane-pretreated MBC.^{3,4} The high single-agent activity and good tolerability of capecitabine makes it an attractive combination partner.

Several surveys have shown that most patients prefer oral treatment instead of intravenous therapy.⁵⁻⁷ Nevertheless, a minority of patients prefer intravenous therapy because they believe that oral therapy

is less effective than intravenous treatment.⁷⁻⁹ We aimed to report the efficacy and toxicity of capecitabine and oral cyclophosphamide combination in anthracycline and taxane resistant MBC patients.

PATIENTS AND METHODS

Between January and September 2007, totally 11 histologically confirmed MBC patients were enrolled into the study. All of them had received anthracyclines and taxanes previously either in metastatic or adjuvant setting. They received capecitabine (1000 mg/m² bid) and oral cyclophosphamide (30 mg/m² tid) on days 1 to 14 every 3 weeks. The chemotherapy continued until progression or intolerance. Depending on the RECIST criteria¹⁰, response to treatment was evaluated with imaging studies every three cycles. Duration of response was calculated by counting the months elapsed from the established response to progression or to analysis time. Toxicity was graded according to the NCI Common Terminology Criteria for Adverse Events version 3.0.

RESULTS

Patient's and tumor characteristics were summarized in Table 1. The median age was 48 years (range, 33-60). All patients had a good performance status (ECOG PS 0-2). All of them had received anthracyclines and taxanes previously either in metastatic or adjuvant setting. Seven patients had received trastuzumab previously, either as monotherapy or as part of combination chemotherapy. The median number of previous chemotherapy lines given was 3 (range: 2-7). The major metastatic sites were lung, bone and liver in order.

Table 1. Patient's characteristics	
Parameter	n
No. of patients	11
Age, years median (range)	48 (33-60)
ECOG performance status	
0	3
1	7
2	1
Menopausal status	
Premenopausal	5
Postmenopausal	6
Hormonal receptor status	
Estrogen receptor (+/-)	5/6
Progesterone receptor (+/-)	4/7
cerbB-2 (+/-/unknown)	7/3/1
Disease at presentation	
Stages I/II/III/IV	0/6/4/1
Predominant metastatic sites	
Liver	2
Lung	5
Bone	4
Previous chemotherapy	
Number of previous lines, median (range)	3 (2-7)
Anthracycline	11
Taxane	11
Trastuzumab	7
Capecitabine	7

Table 2. Response evaluation	
Response	n (%)
Complete	0
Partial	4 (36.4%)
Stable	5 (45.5%)
Progression	2 (18.1%)

Median follow-up was 5 months (range: 2-11). The patients received a median of 8 cycles chemotherapy (range: 2-15). All of 11 patients were evaluated for response: 4 (36.4%) patients achieved a partial response and none had complete response (Table 2). All patients with partial response had received capecitabine monotherapy previously. Median duration of response was 5 (range: 3-8) months. Two (18.1%) patients died related to the disease progression.

Toxicity evaluations are summarized in Table 3. One (9.1%) patient had grade 3 hand-foot syndrome. No grade 4-5 toxicity observed.

Table 3. Toxicity profile				
Laboratory parameter	Number of patients			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Leukopenia	1	2	0	0
Anemia	1	0	0	0
Thrombocytopenia	0	0	0	0
Non-hematological				
Nausea/vomiting	2	0	0	0
Diarrhea	1	0	0	0
Hand-foot syndrome	1	2	1	0
Sensory/motor neuropathy	1	0	0	0
Fatigue	2	0	0	0
AST and/or ALT elevation	2	0	0	0

DISCUSSION

There is no evidence that any specific chemotherapy combination is superior to any other in metastatic breast cancer patients who did not either respond to taxanes and anthracyclines or recurred thereafter. New treatment strategies are increasingly needed for patients failing these therapies or who are at risk of cumulative toxicities. There is no study in the literature investigating the efficacy of the capecitabine and cyclophosphamide combination after taxanes and anthracyclines in MBC patients. Capecitabine has been demonstrated to be effective in this setting with an overall response rate of 9-28%, and overall survival between 9.4 and 15.2 months in several phase II-III trials, either as monotherapy or combination chemotherapy.¹¹⁻¹⁴

In a phase I study investigating the feasibility of the combination of capecitabine (1000-1331 mg/m² on days 1 to 28 every 4 weeks) and oral cyclophosphamide (50-125 mg/m² on days 1-to 14, every 4 weeks), this combination was found to be feasible and tolerable.¹⁵ Shinji et al reported the combination of capecitabine 829 mg/m² bid and oral cyclophosphamide 33 mg/m² bid on days 1 to 14 every 3 weeks to be an active and tolerable regimen.¹⁶ In that study, 16 patients received this combination in the first line, and the overall response rate was 40%. However in our study overall response rate was 36.4% and this rate was achieved in patients with previous taxan or anthracycline exposure (the median number of previous chemotherapy lines was 3). All of our patients with *cerbB2* positive tumors had received trastuzumab. Interestingly patients who progressed on previous capecitabine monotherapy or recurred thereafter responded to the capecitabine and cyclophosphamide combination, cyclophosphamide might have broken the capecitabine resistance. We didnot give the median progression free and median overall survival due to short follow-up. However, the median duration of response was 5 months.

This combination had a very low toxicity profile. No grade 4 to 5 toxicity was observed. Only one grade 3 non-hematological toxicity (hand-foot syndrome) was diagnosed. Toxicity profile in our study is similar to the studies mentioned above.^{15,16}

In conclusion, capecitabine and oral cyclophosphamide combination is a promising and well tolerated regimen in patients who previously had received taxanes and anthracyclines and in patients with *cerbB2* positive tumors who received trastuzumab previously. Patients who were unresponsive to previous capecitabine or who recurred thereafter may respond to capecitabine and oral cyclophosphamide combination.

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Correspondence

Dr. Doğan UNCU
Gülhane Askeri Tıp Akademisi
Tıbbi Onkoloji Bilim Dalı
06018 Etlik ANKARA / TURKEY

Tel: (+90.312) 304 41 74
Faks: (+90.312) 304 41 50
e-mail: doganuncu@yahoo.com