Retrospective Analysis of Capecitabine Monotherapy in Patients with Metastatic Breast Cancer: A Single Center Experience

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ABSTRACT

The aim of this study was to evaluate the efficacy and the toxicity of capecitabine therapy in metastatic breast cancer. A total of 103 patients treated between December 2001 and December 2005 were evaluated retrospectively. Capecitabine was used at a dose of 2500 mg/m²/day for 14 days, with 3 weeks of intervals between cyclesevery 3 weeks. There were 20 patients (19.4%) with brain metastasis at the start of capecitabine regimen. Median cycle of capecitabine was 6 cycles (range 1-24 cycles) mainly as 3rd line therapy (range 1.- 9. line). The overall response rate was 48.6% (3.9% complete response plus 44.7% partial response). The rates of progressive and stable disease were 23.3% and 28.2%, respectively. Thirty patients (29%) required dose reduction due to adverse side effects, and treatment was discontinued in 4 patients (3.8%). Capecitabine is an effective and safe drug in the treatment of metastatic breast cancer, and it has also shown promising activity in the treatment for brain metastases in patients with breast cancer.

Key Words: Metastatic breast cancer, Brain metastasis, Capecitabine

ÖZET

Metastatik Meme Kanserli Hastalarda Kapesitabin Tedavisinin Retrospektif Analizi: Tek Merkez Deneyimi

Çalışmamızın amacı metastatik meme kanserinde kapesitabin kullanımının etkinlik ve toksisite açısından değerlendirilmesidir. Aralık 2001 ile Aralık 2005 tarihleri arasında tedavi edilen toplam 103 hasta retrospektif olarak incelendi. Kapesitabin 2500 mg/m²/gün dozunda, 14 gün boyunca, 3 haftada bir kullanılmıştı. Beyin metastazı olan 20 (%19.4) hasta vardı. Ortanca 3. basamakta (1st.- 9th. basamak arası), ortanca 6 kür (1-24 kür arası) kullanılmıştı. Tüm yanıt oranı %48.6 (tam yanıt oranı %3.9 + kısmi cevap oranı %44.7) idi. Progresif hastalık ve stabil hastalık oranları sırasıyla %23.3 ve % 28.2 idi. Hastaların %29'unda, yan etkiler nedeniyle ilaç dozunda azaltma yapılırken, 4 hastada (%3.8) tedavi kesilmişti. Kapesitabin metastatik meme kanseri tedavisinde etkili ve güvenli bir ilaçtır, beyin metastazı olan meme kanserli hastaların tedavisinde de umut verici etki göstermiştir.

Anahtar Kelimeler: Metastatik meme kanseri, Beyin metastazı, Kapesitabin

INTRODUCTION

Metastatic disease is present in 5-15% of patients with breast cancer.[1] Survival in recurrent disease is related to the location and the extent of metastasis.[2,3] Some patients live for years with metastasis located to a single anatomical region, whereas in others disease rapidly spreads to several organs and causes death in a short time.[4] Survival is relatively short in visceral metastasis, while it is longer in bone and soft tissue metastases.[5-7] Mean survival after recurrence is about 18-30 months.[8] Survival is increasing with the introduction of new agents.[9] Response rate is 20-40% when antracyclines or taxanes are used in monotherapy, whereas this rate increases to 70-80% with combination therapy. In spite of this high activity, progression is inevitable in metastatic breast cancer (MBC). Cure is not possible at this stage of illness. The aims of treatment are to increase survival, eliminate symptoms, improve the quality of life by minimazing toxicity and retard progression.[10] Among agents used after antracyclin and taxane in MBC, there are UFT, liposomal doxorubicine, vinorelbine, mitomycin-C, gemcitabine, cisplatin and combinations of them.[11,12]

Capecitabine is an oral fluoropyrimidine, which is converted to fluorouracil (FU) by a three step enzymatic sequence. The final, rate-limiting step is catalyzed by thymidine phosphorylase (TP). This enzyme hydrolyzes 5-deoxy-5-fluorouridine to the active drug 5-FU. TP is expressed at higher level in some tumors than surrounding normal tissues, resulting in favored intratumor generation of cytotoxic drug. Capecitabine is an oral fluoropyrimidine, developed to create fluorouracil (FU) selectively in neoplasic tissues. It is an effective and safe agent that can be used as in combination with taxanes after an unsuccessful attempt with antracycline containing combination or as monotherapy after antracycline or taxane treatment in patients with advanced local disease or MBC. Patients recieving capecitabine treatment for MBC were evaluated retrospectively, aiming to determine the therapeutic effectiveness and the toxicity of this agent.

PATIENTS AND METHODS

This retrospective study was planned to evaluate the efficacy (overall response rate, duration of response and survival) and safety of capecitabine in patients admitted to the Medical Oncology Outpatient Clinics of Hacettepe University Medical School, Institute of Oncology. Medical records of patients, in whom capecitabine monotherapy was started for MBC at the outpatient clinics of Medical Oncology, were evaluated retrospectively. Charts of 110 patients were reviewed and 103 patients whose data were considered adequate were assessed in terms of response to therapy and drug side effects. The study was approved by the local Ethics Committee (Ethics Committee approval No: LUT 04/64-15).

Capecitabine was administered orally at a dose of 1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period, every 21 days.Capecitabine 1250 mg/m^2 was used in cycles of 21 days, in which it was given twice daily for 14 days, and witheld for 7 days and this This therapy was continued until either a serious toxicity or progression appeared.

Demographic and clinicopathological data was analysed as categorical variables. Staging of every patient was updated according to AJCC 2002 Staging System. Reccurence at the ipsilateral breast, axilla, supraclavicular lymph node, internal mammarian chain, chest wall and skin was considered as local recurrence. Other sites of metastasis were categorized as visceral or bone. Neoadjuvant chemotherapy, adjuvant chemotherapy, adjuvant hormonal therapy, adjuvant radiotherapy applied after diagnosing breast cancer, and treatments done after metastasis occurrence were coded as categoric variables. The date on which capecitabine treatment was started, ended, the date of best response, the date of progression, the date of last follow-up or death were determined and recorded. Overall response rate (ORR) is the primary endpoint in most studies and it is defined as the addition of the number of patients with a complete (CR) and partial response (PR). Side effects were graded between 1-4 points according to general toxicity criteria of the National Cancer Institute of Canada.

A value of $p \leq 0.05$ was considered as statistically significant. 'Statistical Package for Social Sciences (SPSS) 13.0 for Windows' software was used for data analysis.

RESULTS

Characteristics and treatments before capecitabine therapy in the 103 patients are shown in Table 1 and Table 2.

The median number of capecitabine cycles was 6 (range, 1-24 cycles), total number of capecitabine cycles was 670, and median capecitabine administration line was 3rd line therapy (range 1st. - 9th. line). Response rates are shown in Table 3. CR was obtained in 4 patients (3.9%), and PR was obtained in 46 (44.7%), with an ORR of 48.6%. Median time to response was 2.5 months (range, 1.2-15.3 months), median duration of response in patients in whom a respones was obtained was 6.1 months (range, 1.4-20.9 months). The median overall survival (OS) was 17.1 months (95% CI; 11.5 - 22.7). The median progression free survival (PFS) was 6.4 months (95% CI; 4.6-8.1).

The most frequent side effect was the hand-food syndrome (HFS), which developed in 58 patients (56.9%). Of these, 17.2% developed grade 1, 41.4% grade 2 and 41.4% developed grade 3 HFS disease. Diarrhea occurred in 22 patients (21%), nausea in 20 (19%), loss of appetite in 18 (19.6%), vomiting in 16 (15.7%), stomatitis in 15 (14.7%) patients. Myelosupression was seen in 3 patients (2.9%). Dose reduction was required due to adverse effects in 30 patients (29%). Median dose reduction was 25% (range, 8-50%). Capecitabine treatment was stopped in 4 patients (3.8%) because of toxicity. In two of them, diarrhea and grade 3 HFS had occurred concurrently after the 1st cycle, and in the other two patients grade 3 HFS was the reason for stopping treatment. There were no incidents of treatment-related deaths.

Survival rate after capecitabine treatment was analysed for the whole group, according to capecitabine dose modification, hormone receptor and c-erb B2 status, number and site of metastases, and the order of capecitabine in the treatment sequence. The median OS after capecitabine treatment was 17.1 months (95% CI; 11.5-22.7 months), and median PFS was 6.4 months (95% CI; 4.6-8.1 months) (Figure 1A and 1B).

In the survival analysis, no statistically significant difference in OS between the group whose doses were decreased and the group without a dose decrease was observed, but there was a statistically significant difference between these two groups in PFS (8.5% in 1 year in the group without a dose decrease, 36.4% in the group whose doses were decreased, p= 0.007). There was no statistically significant difference in terms of estrogen receptor status and c-erb B2 levels between OS and PFS. There was no difference in OS according to progesterone receptor, but PFS was 63.1% at 6 months in PR-positive patients and 32.4% in PR- negative patients (p= 0.063). The OS of patients in whom dominant metastatis sites were soft tissues, bone and visceral organs were 70.8%, 60.0% and 37% respectively at 18 months (p= 0.019). There was no significant difference between dominant metastasis sites and PFS. The median PFS was 7.3 months in patients with brain metastasis (range, 1.8-26.7 months). The OS in 18 months were 61.3% of the patients with isolated metastasis, 32.8% of the patients with 2 metastasis sites, 59.0% of the patients with 3 metastasis sites and 30.1% of patients with ≥ 4 metastasis sites (p= 0.022). No statistically significant association between the number and sites of metastasis and PFS was detected.

DISCUSSION

Capecitabine is an effective and safe agent, which can be used as monotherapy after antracycline and taxane treatment or in combination with taxanes after an unsuccessful chemotherapeutic regimen containing antracycline in patients with advanced local or MBC. The ORR is 15% - 30% when used as monotherapy and the median OS is about 9.0-19.6 months.[13,14-22] We found an ORR of 48.6%, with median OS of 17.1 months (95% CI; 11.5-22.7 months).

Side effects due to capecitabine treatment are generally mild to moderate in severity. Alopesia and supression of bone marrow are rare. The most frequent side effect is HFS, this being a characteristic skin finding with chronic fluoropyrimidine use. Its pathogenesis is not certain. Like other side effects, HFS rarely requires hospitalization. It can be controlled by lenghtening the time between treatment cycles and decreasing the dose. Patient education about side effects is very important in this regard. The most frequent side effect observed in our study was HFS, which had occurred in 58 patients

Table 1. Characteristics of patients and tumours before capecitabine treatment

	N	%
Total number of patients	103	100
Female / Male	100 / 3	
Age (year) (mean)	46.7 ± 10.6	
Median time between initial diagnosis and beginning of capecitabine therapy (year)	4.0 (0.6-21.9)	
Median time between initial diagnosis and first metastasis (year)	3.0 (0.4-16.0)	
Estrogen and progesterone receptor status		
ER+/PR+	27	26.2
ER+/PR-	14	13.6
ER-/PR+	6	5.8
ER-/PR-	29	28.2
Unknown	27	26.2
Cc-erb B2		
Negative	24	23.3
1-2 +	15	14.6
3+	20	19.4
Unknown	44	42.7
Sites of Metastasis		
Bone	71	68.9
Liver	46	44.7
Soft tissues	38	36.9
Lung	35	34.0
Pleura	24	23.3
Brain	20	19.4
Ovary	5	4.9
Other	10	9.7
Dominant metastasis site		
Soft tissue	18	17.5
Bone	13	12.6
Visceral	70	68.0
Other	2	1.9
Number of metastatic sites before treatment		
1	27	26.2
≥ 2	76	73.8
Capecitabine administration		
First-line	10	9.7
Second-line	19	18.4
Third-line	29	28.2
Fourth-line	22	21.4
Fifth-line	12	11.6
≥ Sixth-line	11	10.7

Abbreviations: ER: Estrogen receptor, PR: Progesterone receptor

Table 2. Treatments before capecitabine therapy (n= 103)

	N	%
Surgical		
Modified radical mastectomy	79	76.7
Radical mastectomy	8	7.8
Simple mastectomy	3	2.9
Lumpectomy + axillary dissection	4	3.9
Lumpectomy	1	1.0
None	8	7.8
Previous chemotherapies		
Anthracycline and taxanes	94	91.3
Docetaxel	81	78.6
Paclitaxel	22	21.4
Docetaxel + paclitaxel	9	8.7
Taxanes, without anthracyclines	1	
Anthracyclines, without taxanes	4	
No anthracyclines or taxanes	4	
Previous 5-FU containing treatment	82	79.6
CMF	30	29.1
Hormonal therapies		
Tamoxifen	70	68.0
Letrozole	42	40.8
Anastrozole	23	22.2
Exemestane	7	6.8
Trastuzumab	5	4.9

Abbreviations: CMF: Cyclophosphamide, Methotrexate, 5-Fluorouracil

(56.9%) (grade 1 in 9.8% and grade 2 and 3 in 23.5%). Myelosupression was observed in 3 patients (2.9%). A reduction in dose was required in 30 patients (29%). Treatment was stopped in 4 patients (3.8%) because of toxicity. In two of them, diarrhea and grade 3 HFS had occurred concurrently after the 1st cycle, and in the other two patients grade 3 HFS was the reason for stopping treatment. The most frequently observed side effects observed in studies of capecitabine in MBC were HFS, mucositis and diarrhea and the frequency of HFS was about 43-56%. [15,17,18,20] Grade 3 was seen in about 9-42%.[14,15,17,18,20,21,23] The doses were reduced in 34-54% of patients, and treatment was stopped in 7-17% of patients.[15,17,18,20] No decrease in efficacy was observed, as in previous studies, after dose reduction due to HFS.[15,17,18,22-25] This suggests that capecitabine may be effective when used in smaller doses than those being currently used (2500 mg/m^2/day), and permits the use of lower doses in patients older than 60 years at the beginning of treatment in order to prevent dose-dependent side effects (e.g.,1900 mg/m^2/day).

The PFS in 1 year was 36.4% in patients whose drug dose was reduced, and 8.5% in those in whom dose was not reduced. As nearly the sole reason for

Table 3. Evaluation of efficacy of capecitabine therapy (n= 103)

	N	%
Complete response	4	3.9
Partial response	46	44.7
Stable disease	29	28.2
Progressive disease	24	23.3
	Time (months)	**Range (months) 95% CI**
Median progression free survival	6.4	4.6-8.1
Median overall survival	17.1	11.5-22.7
Median time to response	2.5	1.2-15.3

dose reduction is HFS in the patient group, this difference may have originated from the association between HFS and PFS. In order for the subgroup data to be more objective, male patients were excluded from the analysis and all women who had at least two cycles of capecitabine were included in the final analysis. Data from a total of 94 women was used. The patients were divided into two groups, those with HFS, n= 55 (58.5%) and those without HFS (n= 39, 41.5%). In subgroup analysis, median PFS in the patients with HFS was 7.1 months (95% CI: 5.3-8.9), and 4.3 months (95% CI: 2.2-6.4) in patients without HFS (p= 0.058).26 But this statistical significance disappeared when OS of the two groups were compared. The median PFS was 6.4 months in patients with grade 1-2 HFS, and 8.4 months in patients with grade 3 HFS (95% CI: 5.7-11.1 months, p= 0.107). Mean OS was significantly higher in the group of patients with grade 3 HFS (29.4 months vs 16.0 months, p= 0.023). These results suggest that HFS occurring during capecitabine treatment is a good prognostic factor for assessment of the efficacy of capecitabine, rather than being a fearsome side effect. Interruption of capecitabine treatment and dose reduction with topical anti-inflammatory medications, pyridoxine, vitamin E, systemic corticosteroids may be used in the treatment of HFS.[27]

We did not find a statistically significant difference between OS and PFS, and presence of ER and c-erb B2 levels in our survival analysis. There was no difference in OS according to PR, whereas PFS was longer in patients with PR (p= 0.063). Although it is a fact that c-erb B2 expression has been regarded as an ominious prognostic factor, we found that c-erb B2 did not have any effects on response to capecitabine treatment in the patients studied.

When the patients were divided into subgroups according to dominant metastasis sites, the OS at 18 months was 70.8%, 60% and 36.6%, respectively with soft tissue, bone and visceral organ metastases, (p= 0.019). Survival was longest in patients with soft tissue metastasis, whereas survival was shorter in patients with visceral metastasis. There was no significant difference in PFS in the survival analysis according to the number of metastasis sites. A better prognosis in patients with soft tissue or isolated organ metastasis is in agreement with the general medical literature.[15]

Patients with brain metastasis were not included in phase II and III studies of capecitabine in MBC.[14,15,17,20,21,24] Successful results in cases with brain metastasis in MBC were reported in several case reports.[28-32] In our group of patients there were 20 with brain metastasis.. The median PFS was 7.3 months in patients with brain metastasis (range, 1.8-26.7 months). There were no significant PFS or OS related differences between patient groups with and without brain metastasis. HFS developed in 11 patients (grade 3 HFS in 5 patients, grade 2 HFS in 4 patients, and grade 1 HFS in 2 patients), and mucositis was seen in one patient. The absence of a significant PFS or OS difference between patients with and without brain metastasis, strenghtens the case for capecitabine being effective and safe for brain metastasis also.

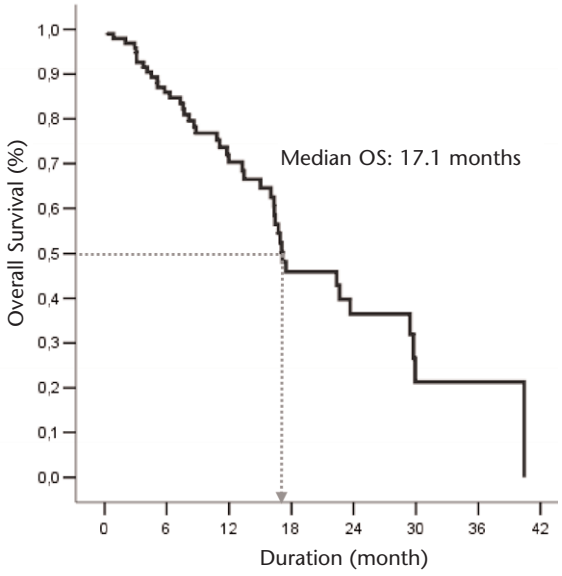

Figure 1A. Kaplan Meier plot for overall survival

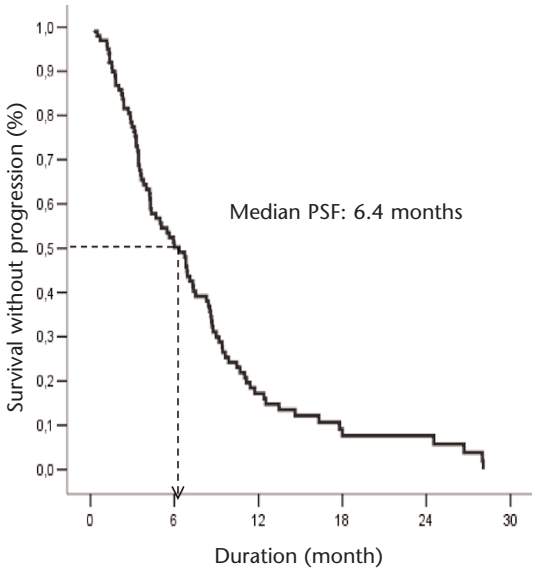

Figure 1B. Kaplan Meier plot for progression free survival

The main aim in the treatment of MBC is to increase survival without decreasing the quality of life. Those medications that increase survival should be used as first line of treatment. For example, gemcitabine and paclitaxel treatments have made possible significant improvement in the time to OS and recurrence. It means that, this combination may be used as first line of treatment. As docetaxel and capecitabine combination was found superior that docetaxel, which has the best response rate in MBC, this combination regiment may be used in early treatment lines in MBC.[24] In first line treatment of MBC, capecitabine was also used in combination with paclitaxel, vinorelbine, gemcitabine and bevacizumab.[16,33-36] The ORR was 30.2-68% and median OS time was 10-29.9 months.

In conclusion, selection of treatment in MBC depends on the patient and tumour characteristics.[37] Aim of therapy is to increase survival together with maximal quality of life.[10] Capecitabine is an effective and good option in MBC, being suitable for oral use, manageable, causing few side effects, and without disturbance of quality of life. Capecitabine is an effective and safe agent in patients who had used several chemotherapeutic regimens such as anthracycline and taxanes and had progressed while using these. Capecitabine is effective in MBC patients with brain metastasis, just like visceral organ metastasis without a difference in the observed side effects.

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