RESEARCH ARTICLE

Lack of Prognostic Value of Mean Corpuscular Volume with Capecitabine Therapy in Metastatic Breast Cancer

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Abstract

Background: Capecitabine is an oral fluoropyrimidine derivative which is frequently used alone or in combination regimens for the treatment of metastatic breast cancer. Although overall and progression free survivals have increased in recent years with the use of new generation drugs, predictive factors that would further improve the outcomes are needed. Previous studies have demonstrated the relation between post-treatment increase in mean corpuscular volume (MCV) and predicting therapy response as well as survival. The present study investigated the clinical impact of MCV elevation in metastatic breast cancer patients treated with capecitabine. Materials and Methods: The data of a total of 82 patients from three centers followed between June 2005 and June 2013 were retrospectively analyzed. The demographic data and hormone receptor status of the patients, as well as initial examination before and after treatment and data concerning progression were recorded. MCV ≥100 fl was considered as macrocytosis. Capecitabine was given at a dose of 2500 mg/m^2 daily for 14 days every three weeks. Pre-treatment and post-treatment MCV and other parameters of complete blood count were recorded. Post-treatment initial evaluation was performed after 2 cycles of therapy. Results: The median age of the patients was 46.5 years (range 26-72 years) and 54% were premenopausal. Performance status was ECOG 0 and 1 in 81 (99%) patients. The median number of cycles for capecitabine therapy was 5 (min-max: 2-18). The median ΔMCV level (post-treatment values at sixth week - baseline) was 6.4. Whilst ΔMCV was ≥6.4 in 42 patients, it was <6.4 in 40 patients. Clinical benefit (complete response+partial response+stable disease) was observed in 37 (88%) of 42 patients with a median ΔMCV ≥6.4 and in 30 (75%) of 40 patients with ΔMCV <6.4 with no statistically significant difference (p=0.158). No significant difference was determined between the group with ΔMCV ≥6.4 and the group with ΔMCV <6.4 in terms of progression-free survival (11 vs 12 months) (p=0.55) and overall survival (20 months vs. 24 months) (p=0.11). Conclusions: The identification of new predictive markers in metastatic breast cancer is very important. In some recent studies, increase in MCV has been suggested as a marker in tumor response. In the present study, however, no significant difference was determined between tumor response and increase in MCV. Further studies including higher numbers of patients are needed to determine whether increase in MCV is a predictive marker or not.

Keywords: Breast cancer - capecitabine - mean corpuscular volume - prognostic factor

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Introduction

Today, the goal of treating metastatic breast cancer (MBC) is to prolong survival and disease control and to provide better palliation to patients. Therapeutic choice in breast cancer depends on certain prognostic and predictive factors including tumor histology, the clinical and pathological features of the primary tumor, axillary node status, hormone receptor content of the tumor, level of HER2/neu, presence or absence of predictable metastatic disease, comorbidities, age and menopausal status of the patient, and patient's choice. Although there has been an increase in overall and progression-free survival with the use of new generation drugs in metastatic breast cancer in recent times, predictive factors that would improve outcomes are needed.

Capecitabine is a pro-drug of 5-FU (Budman, 2000) and was developed based on information that many human tumors contain high concentrations of thymidine phosphorylase. It transforms into active 5-FU in the tumor. Capecitabine, which was approved in 1998 for use in the treatment of patients with metastatic breast cancer which is refractory to anthracycline or taxane therapy, provides an objective response rate of 20-36% and a median survival of longer than 1 year in such patients. It is well-tolerated with the most common side effects including hand-foot syndrome, diarrhea, nausea, vomiting, weakness, myelosuppression and hyperbilirubinemia (Nutley, 2003;

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Pierga et al., 2004; Kurt et al., 2006; Kurt et al., 2009).

Chemotherapeutic agents that blockade DNA synthesis, particularly antimetabolites, cause macrocytosis in the erythrocytes (Hoffbrand and Waters, 1972; Scott and Weir, 1980; Lee, 1993). A limited number of previous studies demonstrated that capecitabine causes macrocytosis in erythrocytes (Wenzel et al., 2003; Karvellas et al., 2004; Arslan et al., 2011; Dellapasqua et al., 2012). In one of these studies, the response rate was found to be higher in patients with elevated MCV under capecitabine therapy (Wenzel et al., 2003). Another study demonstrated that the risk of progression decreased in patients with elevated MCV under capecitabine therapy (Dellapasqua et al., 2012). In the present study, we investigated the relation between change in MCV after capecitabine therapy and therapy response.

Materials and Methods

The data of a total of 82 patients, who had been followed at Erciyes, Gazi and Dicle Universities Departments of Medical Oncology, were retrospectively reviewed. The demographic data and hormone receptor status of the patients, data from pre-treatment and post-treatment initial evaluation, as well as the data concerning progression, were recorded. A complete blood count consisting of hemoglobin, hematocrit, MCV, thrombocyte count, neutrophil count and leukocyte count, which was performed before treatment and during evaluation, was recorded. Response assessment was performed after 2 cycles of chemotherapy (6th week). Evaluation was performed using computed tomography, abdominopelvic ultrasonography, tumor markers and chest x-ray and according to RECIST. Capecitabine was administered at a dose of 2500 mg/m^2 daily for 14 days every three weeks. The lower and upper laboratory reference ranges for hemoglobin and MCV were 11.7-15.5 g/dl and 80.4-95.9 fL respectively. ΔMCV values were calculated by (post-treatment MCV values)-(baseline MCV values). The SPSS (Statistical Package for the Social Sciences) for Windows 15.0 program was used for the statistical analyses. For the analyses of quantitative data, the Student's t-test was used for intergroup comparison of normally distributed data, whereas the Mann Whitney U test was used for intergroup comparison of the data not distributed normally. Was used to determine whether there was a correlation between the parameters by the Pearson-Spearman correlation test. Associations between mcv alteration and clinicopathological parameters were evaluated by chi-square test and Fisher's exact test. Multivariate analysis were done with a logistic regression model. The Kaplan-Meier Log Rank test was used for survival analysis. Results were evaluated within 95% confidence interval and at a significance level of p<0.05.

Results

All of the patients were female. The demographic data of the patients are summarized in Table 1. Whilst dose adjustment was performed in 22 (26.8%) of the patients, the remaining patients continued treatment with the same dose as planned at the beginning. Median dose reduction was 15% (min-max: 10-40). No significant difference was determined between the baseline and 6th week of capecitabine therapy in terms of hemoglobin, thrombocyte, leukocyte and neutrophil counts. Anemia was present in 24 (29.2%) of 82 patients at the onset of capecitabine therapy. Macrocytosis was detected in 5 (6%) patients. All the patients with macrocytosis had normal levels of vitamin B12 and folic acid. The median MCV level was 86.2 (min-max: 71.8-100.1) at baseline and 94.2 (min-max: 78.9-120) on the 6th week of treatment. One patient had an MCV of over 100 fL. MCV increased to over 100 fL in 12 (14.6%) patients at the end of the 6th week.

The median ΔMCV level was 6.4. The ΔMCV level was ≥6.4 in 42 patients and <6.4 in 40 patients. Whilst progression-free survival (PFS) was 12 months (95% CI, 9.79-14.2) in the group with ΔMCV level ≥6.4 and 11 months (95%CI, 8.06-13.9) in the group with a ΔMCV level <6.4 (p=0.55), overall survival (OS) was 24 months (95%CI, 15.1-32.8) and 20 months (95%CI, 8.97-31.02) respectively (p=0.11) (Figure 1). When the patients were grouped as complete and partial response (CR+PR) and stable disease and progressive disease (SD+PD), the median ΔMCV levels were 6.6 (min-max:-2.9-20.3) and 6.3 (min-max:-6.0-17.6) respectively. The difference between the groups was not statistically significant (p=0.58). Association between age, receptor

Table 1. Patient's Characteristics

		N	%
Age, years	Median	46.5	
	Range	26-72	
ECOG PS	0	50	61
	1	31	38
	2	1	1
Menopasual status	Pre-	44	54
	Peri-	7	8
	Post-	31	38
Histopathology	IDC	74	90
	ILC	5	6
	Mixed type	3	4
Sites of metastasis	Viseral	60	73
	Bone	51	62
	Lymph node	8	8
	Other	18	22
Capecitabine treatment	Dose adjustment	22	27
	Median cycles of treatment (min-max)	5 (2-18)	
Receptor status	ER+	35	42
	PR+	34	41
	HER-2 (+++)	6	7
Adjuvant treatment	Chemotherapy (taxanes+anthracyclines)	57	67
	Trastuzumab	6	33

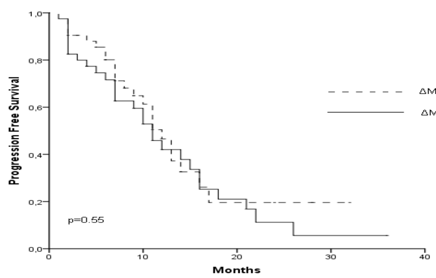

Figure 1. Progression Free Survival (PFS) in ΔMCV Level ≥6.4 vs in ΔMCV Level <6.4

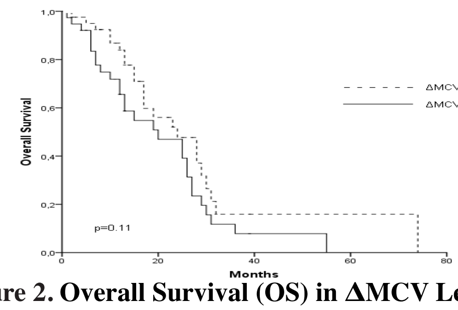

Figure 2. Overall Survival (OS) in ΔMCV Level ≥6.4 vs in ΔMCV Level <6.4

status, menopasual status, body mass index, grading, lympho-vascular invasion, and increased mcv were analyzed using a Cox regression model. Increased mcv was not an independent factor that correlated with OS or PFS (p=0.79 and 0.78, respectively). Clinical benefit (CR+PR+SD) was observed in 37 (88%) of 42 patients with ΔMCV ≥6.4 and in 30 (75%) of 40 patients with ΔMCV <6.4, but the difference was not statistically significant (p=0.158). Whilst the median ΔMCV level was 7.59 (min-max:-0.7-20.3) in the patients that underwent dose reduction, it was 6.3 (min-max:-6.0-17.6) in the group that did not undergo dose reduction (p=0.45). Clinical benefit was observed in 18 (82%) of 22 patients that underwent dose reduction and in 81% of the patients that did not undergo dose reduction (p=1.00).

Discussion

Capecitabine is a fluoropyrimidine carbamate that transforms into 5-FU via 3 enzymatic steps in the liver and tumor cells after oral administration. In the first step, capecitabine is hydrolyzed into 5-deoxy-5-fluorocytidine (5-DFCR) by carboxyl esterase in the liver. In the second step, 5-DFCR transforms into 5-deoxy-5-fluorouridine (5-DFUR) by 5-DFCR cytidine deaminase in the liver and/or tumor tissue. In the third and final step, 5-DFUR is metabolized into active 5-FU by thymidine phosphorylase in the tumor tissue (Takebayashi et al., 1996; Ishikawa et al, 1998a; 1998b; Miwa, 1998). FU turns into fluorodeoxyuridine monophosphate (FdUMP) by thymidine kinase. FdUMP blockades the synthesis of thymidylate by forming a stable tertiary complex with thymidylate synthase (TS) and folic acid and leads to defective DNA synthesis. Prolonged cell cycle due to the decreased thymidylate necessary for DNA synthesis results in over-synthesis of cytoplasmic components including RNA and hemoglobin. This leads to an increase in erythrocyte size and results in macrocytosis (Hoffbrand and Waters, 1972). Therefore, it is likely for the drugs that function via TS inhibition to cause an increase in MCV level.

There are a limited number of studies in the literature evaluating the relation between capecitabine and change in MCV. One of these studies evaluated 67 patients with metastatic breast cancer receiving capecitabine; dose- and duration-dependent MCV elevation was demonstrated with capecitabine therapy. In this study, the presence of macrocytosis was demonstrated with capecitabine in the absence of anemia and other causes of macrocytosis (Karvellas et al, 2004). In their second study, Wenzel et al. (2003) evaluated 154 patients with metastatic carcinoma receiving capecitabine, of whom 41 had breast carcinoma (Wenzel et al., 2003). In this study, vitamin B12, folic acid and homocysteine levels, which are the most common causes of macrocytosis, were checked prior to treatment. They were found to be normal in all patients. In the study, patients were evaluated after 9 weeks and MCV elevation was found to be higher in the patients with complete and partial response (CR+PR) as compared to the patients with stable and progressive disease (SD+PD). Similar findings for response were noted for colorectal cancer cases (Inanc et al., 2014).However, in the present study, when the patients were grouped in the same manner, no significant difference was determined between the groups in terms of change in MCV. Arslan et al. (2011) evaluated 75 metastatic breast cancer patients receiving capecitabine and found the median MCV difference (post-treatment values at nine week-baseline) to be 8. They divided the patients into two groups as MCV difference ≥8 and MCV difference <8. They found the clinical benefit to be better in the group with an MCV difference ≥8. However, no significant difference was found between these two groups in terms of progression-free survival (Arslan et al., 2011). In the present study, the median ΔMCV level was 6.4. When we divided the patients into two groups as ΔMCV ≥6.4 and ΔMCV <6.4, clinical benefit was observed in 88% of the patients with ΔMCV ≥6.4 and in 75% of the patients with ΔMCV <6.4; the difference between the groups was not significant (p=0.158). Moreover, no significant relation was determined among the change in MCV and PFS and OS. In multivariate analysis, increased mcv was not an independent factor that correlated with OS or PFS (p=0.79 and 0.78, respectively).

Any drug that directly or indirectly influences DNA biosynthesis may cause megaloblastic changes by enhancing defective DNA biosynthesis (Scott and Weir, 1980; Lee, 1993; Iacopetta et al., 2001). Fluoropyrimidines may lead to macrocytosis by influencing DNA synthesis. The way in which fluoropyrimidine is applied is important. Daily application for 14 days every three weeks, as in capecitabine therapy, causes prolonged inhibition of TS in the erythrocyte precursors as well as in tumor cells (Schuller et al., 2000; Wenzel et al., 2003). Dellapasqua et al. (2012) conducted a study in 69 metastatic breast cancer patients receiving bevacizumab therapy in combination with metronomic capecitabine and cyclophosphamide and demonstrated decreased risk of progression in the patients that developed macrocytosis (Dellapasqua et al., 2012). In the present study, evaluation was performed after 2 cycles of therapy. If the evaluation had been performed after 3 cycles of therapy, a significant correlation could have been set forth between the change in MCV and therapy response.

Vitamin B12 and folic acid deficiency is the most common cause of macrocytosis. Deficiency of these two vitamins impairs folic acid metabolism and thus DNA synthesis by decreasing thymidylate synthase and causes megaloblastic anemia. In the present study, the concentrations of these two vitamins were found to be within the normal ranges at the beginning of the treatment and during evaluation.

Existing TS polymorphism in erythroid cells might reflect that there is also TS polymorphism in the tumor cells (Pullarkat et al., 2001; Allegra, 2002; Gibson, 2006). In the present study, no statistically significant difference was determined between the group that underwent dose reduction and the group that did not in terms of median MCV difference and clinical benefit. Similar clinical benefit despite lower dose of capecitabine can be explained by TS polymorphism.

In conclusion, the present study found no significant relation among the change in MCV and therapy response, PFS and OS. If the evaluation had been performed on the 9th week instead of the 6th week, a significant relation could have occurred between the change in MCV and therapy response. Larger prospective studies are needed for capecitabine-induced MCV change to be used as a marker for therapy response.

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