

Increased mean corpuscular volume of erythrocytes during capecitabine treatment: a simple surrogate marker for clinical response

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ABSTRACT

Aims and background. Capecitabine, as all fluoropyrimidines, interferes with vitamin metabolism and may thus have an impact on hematopoiesis. It is metabolized to its active form 5-fluorouracil by the enzyme thymidine phosphorylase, which exists in higher concentrations in tumor tissue and liver than in normal tissues. In the study, we investigated the changes in mean corpuscular volume (MCV) of red blood cells and the possible correlation of these changes with the clinical outcome of capecitabine treatment in women with metastatic breast cancer.

Methods and study design. Data from 75 metastatic breast cancer patients were analyzed retrospectively. Capecitabine was used at a dose of 2500 mg/m² daily for 14 days of every 3-week period. Mean corpuscular volume of red blood cells and other parameters of complete blood count were recorded at the beginning of the treatment, in the ninth week, and periodically thereafter.

Results. Mean age was 51.5 ± 10.8 and 61.3% of the patients were premenopausal. Capecitabine was administered as the median 3rd line (min-max: 1-9) treatment and a median of 6 cycles (min-max: 1-24) for metastatic breast cancer. Median ΔMCV level (post-treatment values at ninth week - baseline) was 8. ΔMCV was ≥8 in 37 patients and <8 in 38 patients. The 35 of the 37 patients with ΔMCV level ≥8 and 25 of the 38 patients with ΔMCV level <8 had clinical benefit (complete response + partial response + stable disease) from capecitabine treatment (*P* = 0.02). However, the difference between progression-free survival of the patients with ΔMCV levels higher than 8 and those with ΔMCV levels lower than 8 according to Kaplan-Meier survival analysis was not statistically significant (6.7 and 4.3 months, respectively, *P* = 0.26). Additionally, median ΔMCV level was 9.1 (min-max: -2.4 to 24.9) among patients who had clinical benefit and 5.90 (min-max: -0.8 to 12.3) among nonresponders (*P* = 0.016).

Conclusions. Capecitabine increases the mean corpuscular volume levels of red blood cells by a yet unidentified mechanism. Early increment of mean corpuscular volume levels is higher than 8, i.e. by the 9th week, might predict clinical benefit from the treatment.

Introduction

Capecitabine is a novel oral prodrug that is converted to its active form 5-fluorouracil (5-FU) by a three-step pathway after absorption from the intestine. Carboxylesterase, cytidine deaminase, and thymidine phosphorylase are the enzymes that take part in the activation pathway. Thymidine phosphorylase levels are higher in tumor tissue and liver than in normal tissues. Bioavailability of capecitabine is nearly 100%, and it has a half life ($T_{1/2}$) of 1.5 to 2 hours^{1,2}. Nonetheless, it enables a chronic dosing that mimics continuous infusion of 5-FU³. The cytotoxic effect of the metabolized 5-FU, which arises from defective DNA synthesis, depends on the enzyme thymidylate synthetase. Thymidine kinase converts 5-FU to fluorodeoxyuridine monophosphate, the

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first cytotoxic compound in the metabolic pathway. Fluorodeoxyuridine monophosphate competes with TS and folic acid in the rate-limiting step of de novo thymidine synthesis. DNA synthesis is blocked in the absence of thymidine and cell death ensues. Thymidine phosphorylase also changes 5-FU to fluorouridine triphosphate, which incorporates into RNA. Incorporation of fluorouridine triphosphate results also in inhibition of DNA synthesis, and it induces apoptosis.

Capecitabine is used with high response rates mostly in breast and colorectal cancer, but also has efficacy in several other types of solid tumors including renal cell, prostate, ovarian, gastric and pancreatic carcinoma¹. It is the most effective monotherapy in taxane and anthracycline-resistant metastatic breast cancer (MBC) and also shows efficacy in combination regimens with conventional chemotherapeutics and novel biological agents like trastuzumab, lapatinib or bevacizumab^{1,4-10}. Capecitabine is also well tolerated. Common side effects include nausea, diarrhea, fatigue, the hand-foot syndrome, myelosuppression, and hyperbilirubinemia, which are all moderate¹⁰⁻¹³.

Chemotherapeutics that block DNA synthesis, in particular antimetabolites, are known to cause macrocytosis in red blood cells (RBC)¹⁴⁻¹⁶. There are two previous studies in the literature in which capecitabine was shown to cause macrocytosis in RBC^{17,18}. In one of those studies, higher response rates were observed in solid tumor patients who had increased mean corpuscular volume (MCV) levels under capecitabine treatment¹⁸. Since we observed an increase in MCV of erythrocytes in MBC patients receiving capecitabine treatment, we investigated retrospectively the MCV changes of RBC and the possible relation of these changes with the clinical response.

Method

Demographic, clinical, pathological and laboratory data from 75 MBC patients who received capecitabine in a palliative setting between 2001 and 2005 were evaluated retrospectively.

Complete blood count with differential parameters (including hemoglobin, hematocrit, MCV levels, and platelet, leukocyte, and neutrophil counts) was checked routinely at our clinic prior to starting every cycle of chemotherapy and one week after the start of the first cycle. Response evaluation of the patient under palliative treatment with capecitabine was performed at every three cycles as part of a routine practice at our clinic. From the start date to the evaluation date, this constitutes a time interval of 9 weeks. Chest X-ray, abdominopelvic ultrasonography, and computed tomography scans were performed, and tumor markers were checked after three cycles (at the ninth week of control) of capecitabine treatment. Responses were assessed ac-

ording to WHO criteria¹⁹. MCV increment of the patients receiving capecitabine treatment at the ninth week was found to be correlated with tumor response in the study of Wenzel *et al.*¹⁸

Capecitabine was used at 2500 mg/m² daily for 14 days, every 3 weeks. MCV of RBC and other parameters of complete blood count were checked at the beginning, prior to each cycle of capecitabine, at the ninth week of capecitabine treatment, and periodically thereafter. Δ MCV values were calculated by (post-treatment MCV values) – (baseline MCV values). Time duration from the beginning of capecitabine treatment to the maximum MCV level was also calculated for each patient. Laboratory upper and lower reference values for hemoglobin and MCV were 11.7-15.5 g/dl and 80.4-95.9 fL, respectively.

Statistical analyses were run on SPSS 10.0 for Windows. Parametric tests were used for the numeric variables showing normal distribution, and non-parametric tests were performed for the contrary. For descriptive statistics; “mean \pm standard deviation” is used for the numeric variables with normal distribution and “median (min-max)” for numeric variables that do not show normal distribution and ordinal variables. Student’s *t* test and Mann Whitney-U tests were used for the comparisons. Correlations were analyzed with the Pearson test, and Kaplan-Meier analysis was used for the survival analysis. A statistical significance was assigned when $P < 0.05$.

Results

All of the MBC patients were women. Demographic data of the patients are summarized in Tables 1 and 2. Capecitabine was administered as the median 3rd line (min-max: 1-9) treatment for MBC at a median of 6 cycles (min-max: 1-24). Dose adjustment was made for 24

Table 1 - Characteristics of the patients

| | |
|---|-----------------|
| Age (yr) | 51.5 \pm 10.8 |
| Menopausal status | |
| Pre- | 46 (61.3) |
| Peri- | 3 (4) |
| Post- | 26 (34.7) |
| Adjuvant treatment | |
| Chemotherapy (taxanes + anthracyclines) | 72 (96) |
| Hormone therapy | 26 (35) |
| Trastuzumab | None |
| Sites of metastasis | |
| Visceral | 48 (64) |
| Bone | 21 (15) |
| Soft tissue | 15 (20) |
| Other | 1 (1.5) |
| Capecitabine treatment | |
| Dose adjustment | 24 (32) |
| Median lines of treatment (min-max) | 3 (1-9) |

No. of patients; in parenthesis, percentage.

Table 2 - Characteristics of the patients

| Parameter | No. (%) |
|------------------------|---------------|
| Histopathologic grade | |
| I | 6 (8) |
| II | 20 (26) |
| III | 18 (24) |
| Not known | 31 (38) |
| TNM stage at diagnosis | |
| I/II | 26 (37.1) |
| III | 35 (50) |
| IV | 9 (12.9) |
| Histopathology | |
| IDC | 67 (89.4) |
| ILC | 4 (5.4) |
| Mixed type | 2 (2.7) |
| Receptor status | |
| ER+ | 42 (56) |
| PR+ | 37 (49) |
| HER-2 (++/+++) | 15 (20)/6 (8) |

IDC, infiltrating ductal carcinoma; ILC, invasive lobular carcinoma.

(32%) of the patients, and the remaining received the initial scheduled dose. The median dose reduction made for those patients was 25% (min-max: 10-50%). Leukocyte, neutrophil and thrombocyte counts, and hemoglobin levels between capecitabine treatment start date and week nine were not statistically different from one another. Mean baseline hemoglobin level was 12.5 ± 1.25 and 12.2 ± 1.53 at the ninth week. At the beginning of capecitabine treatment, 23 of the 75 patients had anemia (hemoglobin <12 g/dl), and 6 (8%) of them were macrocytic. All of the 6 patients with macrocytic anemia had normal serum vitamin B12 and folate levels.

Median baseline MCV level was 85.7 (min-max: 68.1-98.7) and 94.2 ± 7.3 (min-max: 71.1-112.1) fL at the ninth week. None of the patients' baseline MCV levels were higher than 100 fL. However, MCV levels increased to ≥ 100 fL in the ninth week in 14 (18.6%) of the patients.

MCV levels increased in all but 3 patients, and MCV level of one patient did not change at the ninth week. However, MCV levels all of these four patients increased at the later follow-up. None of these patients had anemia and/or microcytosis. At response evaluation; 2 of the patients in whom MCV level decreased at the ninth week showed partial remission (PR) and one showed progressive disease (PD). The patient in whom MCV level did not change at the ninth week had stable disease (SD).

Median Δ MCV level was 8 at week nine. Δ MCV was ≥ 8 in 37 patients and <8 in 38 patients. Thirty-five of the 37 patients with Δ MCV levels ≥ 8 and 25 of the 38 patients with Δ MCV levels <8 had a clinical benefit (complete response, CR, + PR + SD) from capecitabine treatment ($P = 0.02$) (Figure 1). However, the difference between progression-free survival of the patients who had Δ MCV ≥ 8 and those who had <8 was not statistically significant, according to Kaplan-Meier survival analysis (6.7 and 4.3 months, respectively, $P = 0.26$) (Figure 2).

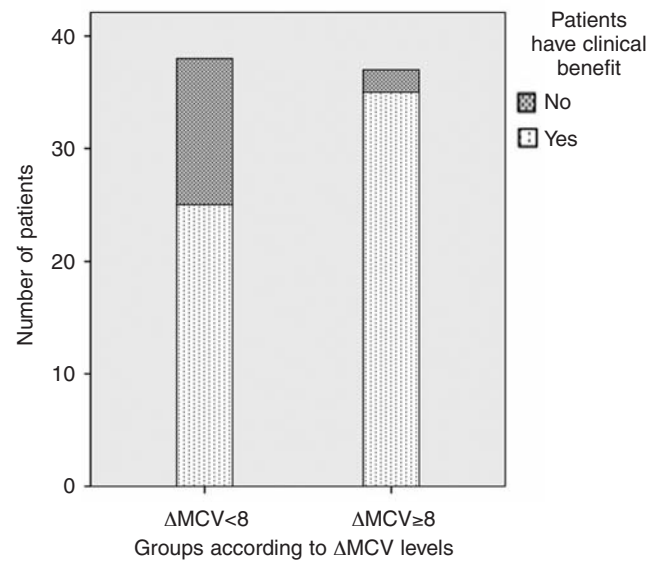


Figure 1 - The number of patients who had a clinical benefit was higher in Δ MCV ≥ 8 than Δ MCV <8 group. Δ MCV = (MCV at 9th week) - (baseline MCV). Patients with a clinical benefit, those with complete response + partial response + stable disease; patients who did not have a clinical benefit, those with progressive disease. MCV, mean corpuscular volume.

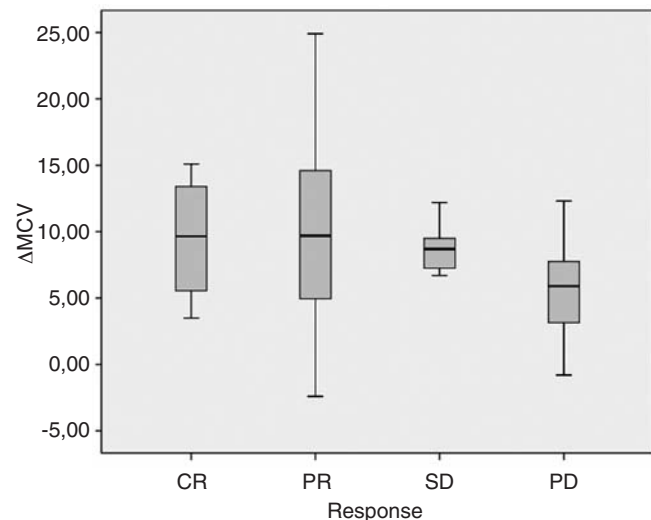


Figure 2 - Δ MCV = (MCV at 9th week) - (baseline MCV). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. Δ MCV levels of the patients were higher in patients with clinical response (CR + PR) and SD than in those who did not show any response. MCV, mean corpuscular volume.

Median Δ MCV level was 9.1 (min-max: -2.4 to 24.9) among patients with clinical benefit (CR + PR + SD) and 5.90 (min-max: -0.8 to 12.3) among nonresponders ($P = 0.016$) (Figure 3).

Median Δ MCV levels of patients in whom a drug dose reduction was made were 10.3 (min-max: 1.7-24.9) and 7.6 (min-max: -2.4 to 19.2) in whom a dose reduction was not made ($P = 0.04$). Clinical benefit rate was 88% for patients in whom dose reduction was made and 77%

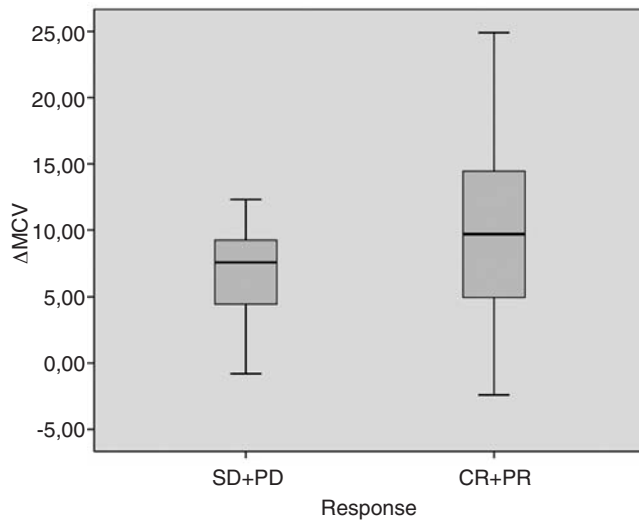


Figure 3 - Δ MCV levels of patients with CR (complete response) and PR (partial response) were higher than in patients with SD (stable disease) and PD (progressive disease). MCV, mean corpuscular volume.

for patients in whom dose reduction was not made ($P = 0.36$). Twenty-one of 24 patients whose drug doses were reduced had clinical benefit. Median Δ MCV levels of the patients in whom drug dose was reduced were 10.5 (min-max: 1.7-24.9) and 4.7 (min-max: 1.9-11.6) for patients with and without clinical benefit, respectively ($P = 0.18$). Sixteen of 17 (94%) and 5 of 7 (71%) patients had clinical benefit, and Δ MCV was above 8 and below 8, respectively ($P = 0.19$).

When patients were grouped as partial and complete responders (CR + PR) and patients with stable and progressive disease (SD + PD), median Δ MCV level was 9.7 (-2.4 to 24.9) and 7.6 (-0.8 to 17.9), respectively ($P = 0.047$) (Figure 4).

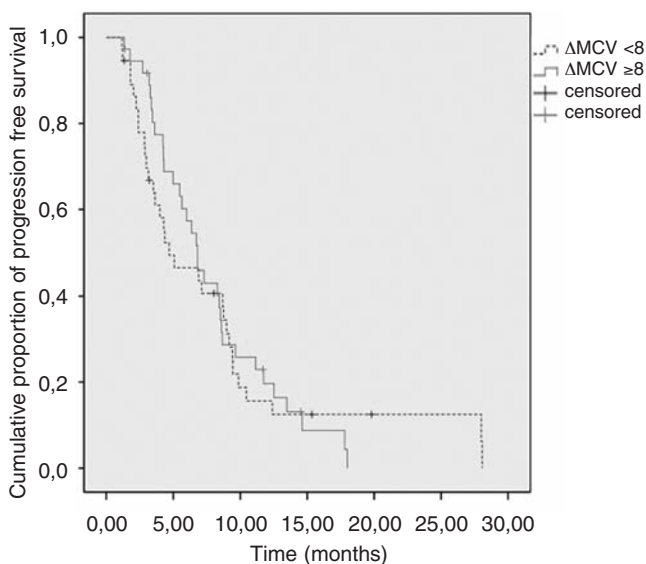


Figure 4 - There was no difference between progression-free survival (PFS) of patients with Δ MCV ≥ 8 and Δ MCV < 8 . MCV, mean corpuscular volume.

Mean maximum MCV level under capecitabine treatment was 98 fL (min-max: 71.1-114.2) and mean duration time from the start date of capecitabine treatment to the maximum MCV level was 136 days (min-max: 30-534). Maximum MCV levels were higher than 100 fL in 30 of 75 (40%) patients. There was no statistically significant correlation between Δ MCV and time to the maximum MCV level.

Discussion

In our study, we found that the clinical benefit rate was higher in patients with Δ MCV ≥ 8 than in those with Δ MCV < 8 , under capecitabine treatment for MBC. However, there was no significant difference in progression-free survival of patients with Δ MCV ≥ 8 and those < 8 . Δ MCV level was higher among patients who had a clinical benefit than in nonresponders. Δ MCV level was also higher among patients who showed a PR and CR than in those with SD and PD.

Given our clinical observation of an MCV increase in capecitabine-treated MBC patients and a potential relationship with clinical response to the treatment, we searched the literature for data on MCV changes and capecitabine treatment. We found two previous reports in the English literature concerning this issue^{17,18}. One of the two studies was conducted on 67 breast cancer patients receiving capecitabine¹⁷. However, the study was not designed for investigation of response to chemotherapy. In the trial, capecitabine therapy was shown to produce time- and dose-dependent macrocytosis in MBC patients. However, macrocytosis was not found to be associated with anemia or overt myelosuppression. It was concluded that when capecitabine-treated breast cancer patients developed macrocytosis, in the absence of anemia, investigation of other causes of macrocytosis was not warranted¹⁷. The second trial was conducted on 154 advanced cancer patients under capecitabine treatment and 41 of them had breast cancer¹⁸. Vitamin B12, folate, and homocysteine levels were checked to rule out the frequent causes of macrocytosis and were in normal ranges in all of the patients. The cut-off time of nine weeks was taken for evaluation, as done in our study. In accord with our findings, the increase in MCV levels was higher in patients with tumor response (CR + PR) and SD than in those with PD.

In our study, MCV levels of 4 patients showed a delayed increase from the baseline levels (later than the ninth week). MCV levels decreased in three and did not change in one of them at the ninth week. Two of the patients in whom MCV level decreased at the ninth week showed PR (Δ MCV = 8.5 at the 15th week and Δ MCV = 10, at the 10th week) and one showed PD (Δ MCV = 1 at 12th week), and the patient in whom MCV level did not change at the ninth week had SD (Δ MCV = 2 at the 12th week). As none of these patients had anemia, ferritin

levels and serum iron markers were not checked. Thus, decreased MCV levels in 3 patients and stable levels in 1 patient could not be explained.

An increase of 8 fL might be a cutoff value for predicting an early response to capecitabine treatment according to the results of our study. None of the patients had MCV levels higher than 100 fL at the start date of capecitabine treatment. However, 18.6% and 40% of the patients had MCV >100 fL at the ninth week and at the date of the maximum MCV level (mean, 136 days), respectively. The number of patients in whom MCV was above 100 fL increased with time. Such a finding was similar to that found in the study of Karvellas *et al.*¹⁷ However, detection of early increase in MCV is important for predicting treatment response.

The exact mechanism of MCV increment in patients on capecitabine treatment is not known. However, treatment with any drug which affects DNA biosynthesis directly or indirectly may cause megaloblastic changes, and increased MCV may be an expression of defective DNA biosynthesis^{15,16,20}. Antipurine medications have been reported to result in megaloblastic anemia, likely as a result of defective DNA synthesis¹⁵. Fluoropyrimidines also interact with DNA synthesis and may cause macrocytosis. Wenzel *et al.*¹⁸ suggested that an increased MCV (without concomitant anemia) in patients receiving capecitabine might be due to the 5-FU-induced TS inhibition in erythroid precursor cells, as well. Administration regimens of fluoropyrimidines might be important at that point, i.e., continuous by oral capecitabine therapy for 14 days.

The most frequent cause of macrocytic anemia seen in clinical practice is vitamin B12 or folate deficiency. These two vitamin deficiencies appear to cause megaloblastic anemia by impairing folate metabolism and subsequently impairing DNA synthesis by reducing thymidylate synthetase. The cell cycle prolongs with this impairment while the synthesis of intracytoplasmic molecules goes on and accumulates. Such accumulation might be responsible for the macrocytic anemia in vitamin B12 and folate deficiency¹⁴. Similarly, inhibition of thymidylate synthetase is the mechanism of action for cytotoxic activity of capecitabine¹. The same mechanism observed in patients with folate or vitamin B12 deficiency might be responsible for the MCV increase in patients under capecitabine treatment. Continuous exposure to capecitabine such as; 14 days in every 21 days in routine treatment regimens might cause continuous and prolonged inhibition of thymidylate synthetase in tumor as well as in erythroid cells. Continuous oral administration of capecitabine acts differently on thymidylate synthetase than intravenous bolus 5-FU^{21,22}. However, infusional regimens of 5-FU must be evaluated for this effect¹⁸.

One of the possible mechanisms of differences in MCV increase might be thymidylate synthetase polymorphism which will affect both cytotoxic effect on tumor

cells and MCV increase of RBCs^{20,23,24}. However, we do not know exactly that the same polymorphisms at normal tissue i.e. erythroid precursors was represented by thymidylate synthetase polymorphisms at tumoral tissue. In this study, median Δ MCV of drug dose reduced patients was higher than of patients drug dose was not changed. But clinical benefit rates were similar in both groups. Twenty-one of 24 dose reduced patients had clinical benefit and median Δ MCV in these patients was higher than patients did not have clinical benefit (10.5 vs 4.7; $P = 0.18$). It might be possible to observe an increased MCV and clinical benefit also in patients receiving low doses of capecitabine, probably due to thymidylate synthetase polymorphism. One of the limitations of our study is that since it was a retrospective study, vitamin B12, folic acid, homocysteine, and methyl-malonic acid levels were not checked for all of the patients. However, at the start date of capecitabine treatment there were 23 patients that had anemia and 6 of them were macrocytic. The rest of the patients ($n = 17$) had normocytic or microcytic anemia and, hemoglobin levels of 52 patients were not below normal limits. Vitamin B12 and folic acid levels were normal in those patients with macrocytic anemia. Microcytic or normocytic anemia is seen less frequently in vitamin B12 and folic acid deficiency compared to macrocytic anemia. As a common knowledge; folic acid deficiency develops in months and vitamin B12 deficiency in years and, nine weeks is not long enough to develop deficiency of these vitamins that were considered to be at normal levels at baseline. Thus, we might suppose that none of the patients had low levels of vitamin B12 and folic acid at the ninth week control.

In conclusion, capecitabine increases the MCV levels of RBCs. Early increment of MCV levels i.e. 9th week might predict the clinical benefit from treatment. However, there was no significant difference in progression-free survival between patients with high or low Δ MCV. Further prospective studies with large numbers are needed for determining the correlation between the changes in MCV with capecitabine treatment and tumor response.

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