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ORIGINAL ARTICLE

Capecitabine-related increased mean corpuscular volume of red blood cell may be a predictive marker of treatment response and survival in patients with metastatic colorectal cancer

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Summary

Purpose: *Erythrocyte mean corpuscular volume (MCV) increase has been described in patients treated with capecitabine. In this study, we sought to evaluate the potential association of the erythrocyte MCV increase with tumor response and survival in patients with metastatic colorectal cancer (mCRC) treated with capecitabine.*

Methods: *A retrospective review of 131 patients with mCRC who were treated with capecitabine for at least 3 months at the Izmir Training and Research Hospital was undertaken. Complete blood count (CBC) including red blood cell indices were recorded at baseline and after 9 weeks from capecitabine treatment.*

Results: *The mean patient age was 57.9 years (range 28-82). In patients treated with capecitabine, MCV increased significantly at 9 weeks compared with baseline (p=0.000). Median ΔMCV [(post-treatment MCV values) – (baseline MCV values)] level was 9.3 fL. Patients were grouped according to ΔMCV into two groups (> 9.3 or ≤ 9.3) in order to carry out survival analysis and correlation with tumor response. ΔMCV was >9.3 in 65 patients and ≤9.3 in 66 patients. Fifty-six of the 65 patients with ΔMCV levels >9.3 and 37 of the 66 patients with ΔMCV levels ≤9.3 had a clinical benefit (complete response + partial response + stable disease) from capecitabine treatment (p=0.000). The difference between progression-free survival (PFS) and overall survival (OS) of the patients who had ΔMCV>9.3 and those who had ≤9.3 was statistically significant (9.48 and 6.94 months, p=0.001 respectively; and 17.5 and 13.6 months respectively, p=0.018). Univariate analysis suggested that a favorable prognosis for OS and PFS was associated with MCV increase (p=0.000). In multivariate analysis, MCV increase was independently associated with favorable survival outcomes.*

Conclusions: *Erythrocyte MCV increase may be used as a predictive marker for treatment response, PFS and OS in patients with mCRC treated with capecitabine.*

Key words: *capecitabine, erythrocytes, mean corpuscular volume, metastatic colorectal cancer, response, survival*

Introduction

CRC ranks third as cause of cancer-related deaths in both sexes, despite the improvement in prognosis and survival of mCRC in recent years [1]. So far, many chemotherapeutic agents such as irinotecan and oxaliplatin have been introduced in the treatment of mCRC but 5-fluorouracil (5-FU) has remained the standard chemotherapeutic agent. Because capecitabine mimics 5-FU, it potentially offers a more favorable alternative to i.v. 5-FU therapy. Clinical trials have shown that capecitabine is an effective and tolerable therapy for mCRC, achieving response rates of 26% and similar PFS and OS compared with i.v. 5-FU/leukovorin (LV) [2-5]. Furthermore, capecitabine is associated with a low rate of side effects compared with infusional or bolus regimens. The most common side effects are nausea, diarrhea, fatigue, hand–foot syndrome, myelosuppression and increase in serum bilirubin [6]. Also, an interesting capecitabine-related adverse effect is mac-

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rocytosis that has been reported in several studies [7-10].

We performed a retrospective review of mCRC patients receiving oral capecitabine therapy for mCRC and evaluated whether capecitabine therapy might be accompanied with increase in MCV. Furthermore, we sought to explore the potential association of capecitabine related macrocytosis with tumor response, PFS and OS in Turkish patients with mCRC.

Methods

After obtaining permission from the Institutional Ethics Committee, we retrospectively reviewed the data of 131 patients with mCRC treated with capecitabine in a single institution between January 2005 and December 2012. The patients were observed until July of 2013.

Eligibility criteria

The eligibility criteria for study inclusion were histologic documentation of adenocarcinoma of the colon or rectum; adequate hematological and hepatic (serum total bilirubin <1.5 mg/dl and AST/ALT <3 the upper limit of normal/ULN) functions; WHO performance status (PS) 0-2; age 18-80 years; and no previous chemotherapy for metastatic disease. Previous adjuvant chemotherapy was required to have been completed at least 6 months before inclusion.

Chemotherapy

All patients received a capecitabine-containing regimen as first line therapy, either as monotherapy or in combination with other antineoplastic agents. Adjuvant or neoadjuvant therapy completed at least 6 months prior to enrollment was permitted. The combination of oxaliplatin or irinotecan with capecitabine, as described by XELOX and XELIRI, alongside bevacizumab was used. XELOX consisted of a 2-h intravenous infusion of oxaliplatin 85 mg/m^2 on day 1 plus oral capecitabine 1,000 mg/ m^2 twice daily on days 1 to 14 every 3 weeks. XELIRI consisted of a 2-h intravenous infusion of irinotecan 185 mg/m^2 on day 1 plus oral capecitabine 1,000 mg/m^2 twice daily on days 1 to 14 every 3 weeks. Bevacizumab at a dose of 7.5 mg/kg was administered as a 30- to 90-min intravenous infusion on day 1 of the 3-week cycle.

Complete blood count, including hemoglobin, hematocrit, MCV, MCH, MCHC levels, and platelet, leukocyte, and neutrophil counts were checked routinely prior to starting each cycle of chemotherapy and particularly at the 9th week of capecitabine treatment. Cut off time was the 9-week period, as has been done in other reports. ΔMCV values were calculated (post-treatment MCV values) – (baseline MCV values). The time from the beginning of capecitabine treatment to disease progression or death were also calculated for each patient.

Response evaluation

Response evaluation was performed every 3 cycles. Computed tomography scans were performed, and tumor markers were checked after 3 cycles of capecitabine treatment. Responses were evaluated according to the RECIST criteria [11]. Patients included in this analysis were categorized on the basis of their best tumor response as either responders (patients showing complete or partial response or stable disease) or nonresponders (patients with progressive disease). The response rate was defined as the proportion of patients who achieved a complete or partial response or stable disease after the initiation of treatment. The sites and date of relapse and the date of death were recorded. Patients were divided into two groups according to ΔMCV (>9.3 or ≤9.3) in order to carry out survival analyses and correlation with tumor response.

Statistics

Within an exploratory analysis the patient cohorts were compared using Fisher's exact test, and x^2-test for proportions. PFS and OS were evaluated using the Kaplan–Meier method and log-rank test. OS was defined as the time from the date of the first capecitabine administration to the date of death or last follow-up visit. PFS was calculated from the first capecitabine administration to tumor progression or last follow-up visit if not progressed. The factors related to survival were analyzed. Multivariate analysis was performed using Cox regression model (Cox proportional hazards model) with forward stepwise selection of covariates and with enter and remove limits of $p<0.05$ and $p>0.10$, respectively. Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated. Statistical analysis was carried out using MedCalc software package (MedCalc®-v.16.0). A level of 0.05 was chosen to assess statistical significance.

Results

Patient characteristics are shown in Table 1. The mean patient age was 57.9 years (range 28-82), and 99 patients (76%) were aged >50 years. At the end of follow-up (mean 26.9 month, maximum 116 months), 54 (41.2%) study patients had died.

Capecitabine was administered as first line treatment. Fourteen patients received capecitabine in combination with irinotecan. Twenty-seven patients received capecitabine in combination with oxaliplatin. Sixty-three patients received 7.5 mg/kg bevacizumab in combination with XELIRI. Twenty-seven patients received 7.5 mg/kg bevacizumab in combination with XELOX.

Table 1. Patient baseline characteristics

Characteristics	*N (%)*
Total number	131 (100)
Male/female	73/58 (55.7/44.3)
Age (years)	
Median	60
Range	28-82
Primary tumor site	
Colon	42 (32)
Rectosigmoid	89 (68)
Stage at diagnosis	
II-III	47 (35.8)
IV	84 (64.2)
Grade	
1	5 (3.8)
2	89 (67.9)
3	37 (28.2)
Positive lymph nodes	
None	59 (45.0)
1-4	48 (36.6)
5-9	12 (9.1)
≥10	12 (9.1)
Number of metastatic sites	
None	47 (35.8)
1	74 (56.4)
2	7 (5.3)
≥3	3 (2.2)
Sites of metastases	
Liver	59 (45.0)
Lung	47 (35.8)
Bone	2 (1.5)
Peritoneum	12 (9.1)
Regimen	
XELOX	27 (20.6)
XELIRI	14 (10.6)
XELOX+Bevacizumab	27 (20.6)
XELIRI+Bevacizumab	63 (48.0)

For regimens' details see text

Prior to capecitabine treatment, there were no abnormalities in red blood cells, white blood cells, platelets, hemoglobin, MCH, MCHC and did not change significantly after the 9-week treatment. Median hemoglobin levels (normal range 12–16 g/dl) were 12.1 g/dl, MCV (normal range 78–98 fl) was 84.5 fl, MCH (normal range 27–33 pg) was 28.2 pg and MCHC (normal range 32–36 g/dl) was 33.2 g/dl before treatment. None of the patients' baseline MCV levels were higher than 100 fL. After 9 weeks, a statistically significant increase of MCV could be observed up to 93.7 fl (p=0.000). MCV levels increased to ≥100 fL in the 9th week in 21 (16%) patients.

Table 2. Influence of MCV on tumor response, PFS and OS

ΔMCV value	*Tumor response and survival (mo) N (%)*	*p-value*
ΔMCV > 9.3	56/65 (86.2)	0.000
ΔMCV ≤ 9.3	37/66 (56.1)	
	Median PFS 5 (range 3-30)	
ΔMCV > 9.3	9.48	0.001
ΔMCV ≤ 9.3	6.94	
	Median OS 23 (range 3-116)	
ΔMCV > 9.3	17.5	0.018
ΔMCV ≤ 9.3	13.6	

PFS: progression free survival, OS: overall survival, mo: months, MCV: mean corpuscular volume, ΔMCV: (post-treatment MCV values)-(baseline MCV values)

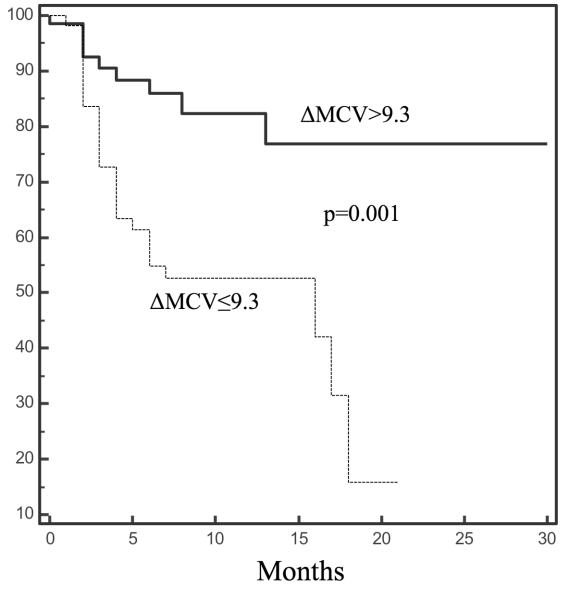

Figure 1. Progression free survival of metastatic colorectal cancer patients with ΔMCV > 9.3 and ΔMCV ≤ 9.3.

Median ΔMCV [(post-treatment MCV values) – (baseline MCV values)] level was 9.3 and this value was determined as the cut-off. ΔMCV was >9.3 in 65 patients and ≤ 9.3 in 66 patients. Fifty-six of the 65 patients with ΔMCV levels >9.3 and 37 of the 66 patients with ΔMCV levels ≤9.3 achieved clinical benefit (complete response+partial response+stable disease) from capecitabine treatment (p=0.000) (Table 2). The difference in PFS between patients who had ΔMCV >9.3 and those who had ≤ 9.3 was statistically significant, according to Kaplan-Meier survival analysis and log rank test (9.48 and 6.94 months, respectively, p=0.001) (Table 2, Figure 1). The difference in OS between patients who had

Table 3. Univariate analysis of variables affecting progression free and overall survival

Variables	*N*	*Median OS (mo)*	*p-value*	*Median PFS (mo)*	*p-value*
Total	131	35		9	
Age (years)			0.950		0.763
< 50	32	33		9	
> 50	99	31		9	
Gender			0.116		0.536
Male	73	31		9	
Female	58	42		9	
Stage			0.000		0.041
II	20	42		14	
III	27	45		12	
IV	84	24		7	
Tumor location			0.016		0.176
Right colon	23	25		9	
Left colon	13	36		12	
Rectosigmoid	89	33		8	
Transverse colon	6	45		4	
Grade			0.534		0.067
I	5	34		14	
II	89	29		11	
III	37	32		6	
Positive lymph nodes			0.968		0.873
None	59	31		8	
1-4	48	32		9	
5-9	12	24		9	
≥10	12	27		6	
Kras			0.466		0.590
Wild	45	28		7	
Mutant	24	36		8	
Unknown	62	27		9	
ΔMCV			0.000		0.010
≤ 9.3	66	27		7	
> 9.3	65	42		10	
Treatment regimen			0.000		0.230
XELIRI	14	83		11	
XELOX	27	42		7	
XELIRI+Bev	63	33		12	
XELOX+Bev	27	17		7	
Treatment response			0.461		0.000
Complete response	18	31		14	
Partial response	57	31		11	
Stable disease	20	33		7	
Progressive disease	36	31		3	

mo: months. Bev: bevacizumab, OS: overall survival, PFS: progression free survival, MCV: mean corpuscular volume. For regimens' abbreviations see text

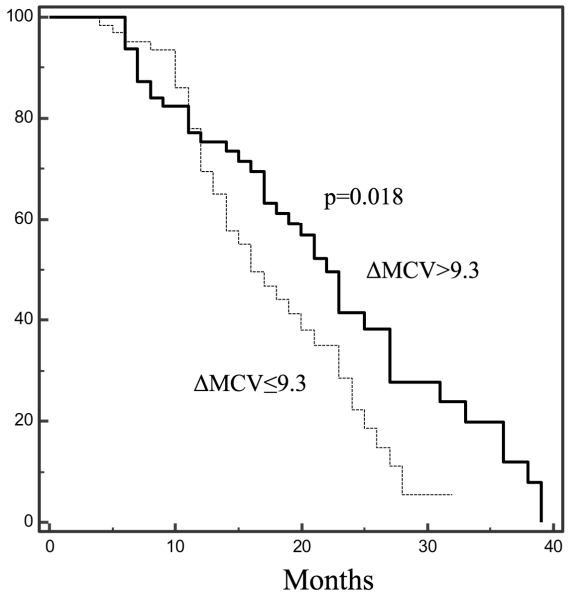

Figure 2. Overall survival of metastatic colorectal cancer patients with ΔMCV > 9.3 and ΔMCV ≤ 9.3.

ΔMCV >9.3 and those who had ≤ 9.3 was statistically significant, according to Kaplan-Meier survival analysis (17.5 and 13.6 months, respectively, p=0.018) (Table 2, Figure 2).

Univariate analysis of potential prognostic factors affecting survival

Ten variables were analyzed (Table 3). Univariate analysis suggested that a favorable prognosis for OS was associated with the following 4 variables: (1) stage of tumor at diagnosis time (p=0.000); (2) location of tumor (p=0.016); (3) ΔMCV (p=0.000); and (4) regimen of chemotherapy (p=0.000). The remaining 6 variables did not demonstrate any significant impact on OS. In univariate analysis, stage of tumor at diagnosis (p=0.041), ΔMCV (p=0.01) and treatment response (p=0.000) were significantly related with PFS.

Multivariate analysis of potential prognostic factors affecting survival

Four of these 10 variables assessed in the univariate analysis entered into the Cox multivariate regression model (Table 4). Multivariate analysis showed that stage of tumor at diagnosis (p=0.000, HR=0.193), tumor location (p=0.003, HR=3.191), ΔMCV (p=0.009, HR=2.324) and regimen of chemotherapy (p=0.001, HR=1.150) were independent predictive factors for OS. Furthermore, 4 factors were independently associated with a favorable PFS: stage of tumor at diagnosis (p=0.000, HR=0.314), ΔMCV (p=0.047, HR=0.608), regimen of chemotherapy (p=0.029, HR=2.210) and treatment response (p=0.000, HR=0.270).

Discussion

The current analysis confirms previous reports that increase of MCV is a indicator of tumor response in patients treated with capecitabine [7-10].

Table 4. Multivariate analyses of factors affecting PFS and OS with Cox Proportional Hazards Regression Models in patients treated with capecitabine

	Disease free survival		*Overall survival*	
Factors	*Hazard ratio (95% CI)*	*p-value*	*Hazard ratio (95% CI)*	*p-value*
ΔMCV				
> 9.3	0.608 (0.372-0.994)	0.047	2.324 (1.230-4.393)	0.009
≤ 9.3	1		1	
Stage				
II - III	1		1	
IV	0.314 (0.176-0.561)	0.000	0.193 (0.091-0.408)	0.000
Tumor location				
Colon	1		1	
Rectosigmoid	0.894 (0.306-2.609)	0.119	3.191 (0.666-15.292)	0.003
Treatment regimen				
XELIRI / XELIRI+Bev	2.210 (0.779-6.270)	0.029	3.658 (1.739-7.694)	0.001
XELOX / XELOX+ Bev	1		1	
Treatment response				
CR/PR/SD	0.270 (0.160-0.454)	0.000	1.324 (0.678-2.585)	0.411
PD	1		1	

For treatment regimens and other abbreviations see text

In addition, Cox regression multivariate analysis showed that increase of MCV is an independent predictor of better OS and PFS. Considering the results of studies with capecitabine, in none of them was PFS and OS a prognostic factor [7-10].

Capecitabine, which is an oral fluoropyrimidine, has been one of the most searched agents recently because of its favorable results in CRC regarding both efficiency and safety. When capecitabine was given as both first and second-line treatment for mCRC, benefits similar to bolus or infusional 5-FU [2,5,12-15] were obtained; the same was true when capecitabine was administered as adjuvant therapy for stage III colon cancer [16]. Recently, it was shown that capecitabine can be effective in the neoadjuvant setting for locally advanced rectal cancer [17]. Furthermore, medical resource use analysis showed that patients treated with capecitabine spent fewer days in hospital for the management of treatment-related adverse events compared with patients treated with parenteral 5-FU/LV [18].

Capecitabine is a prodrug designed to mimic the effects of infusional 5-FU. This agent has a DNA-directed toxicity induced by thymidilate synthetase (TS) inhibition [19]. After oral administration, capecitabine is rapidly and completely absorbed through the gastrointestinal wall [20]. A three-step enzymatic process is necessary to convert capecitabine to the active drug 5-FU. The third step is mediated by thymidine phosphorylase, an enzyme frequently expressed in tumor tissues [21]. Thus, the tumor selectivity of capecitabine reduces systemic exposure to 5-FU and potentially improves efficacy and safety [13,21]. The most common capecitabine-related side effects, including nausea, vomiting, diarrhea, myelosuppression, and hand-foot syndrome usually have mild-to-moderate intensity [20,21]. An interesting side effect due to capecitabine was macrocytosis that has been previously reported in patients treated with capecitabine in several malignancies, including particularly breast cancer. In a retrospective review on 76 metastatic breast cancer patients receiving oral capecitabine therapy, 57% of the study patients developed macrocytosis. Karvellas et al. showed that capecitabine therapy causes time-dependent and dose-dependent macrocytosis [8]. Whereupon we performed a retrospective analysis of this side effect and the relationship between macrocytosis and treatment outcome in terms of tumour response, PFS and OS in mCRC patients. Our study showed that MCV increase was statistically significantly greater in the patient group with complete, partial or stable treatment responses compared with patients showing progression. Also, in the paper by Wenzel et al. higher MCV values were seen in patients with complete and partial tumor responses than in patients with tumor progression, but no survival advantage could be demonstrated [7]. In the study carried out by Arslan et al. in patients with breast cancer treated with capecitabine, MCV increase was also found to be correlated with clinical response [8]. In the study by Dellapasqua et al. in patients with breast cancer, significant results regarding both treatment response and PFS were obtained, similar to our study [10].

Macrocytosis is divided into 2 categories: megaloblastic and nonmegaloblastic. Megaloblastic macrocytosis results most commonly from vitamin B12 or folate deficiency. Vitamin B12 deficiency and impaired folate metabolism reduce thymidylate synthesis. The formation of cell DNA from thymidylate is therefore slowed down and this is responsible for the increased size of the cells in megaloblastic changes and macrocytic anemia [22]. The measurement of serum factors such as vitamin B12 and folate was not undertaken in our patients. In the report by Karvellas et al. vitamin B12, folate and homocysteine levels were within normal range in all of the patients and the authors did not recommend the measurement of their levels as long as there is no anemia [8]. Nonmegaloblastic causes of macrocytosis are liver disease, hypothyroidism, alcoholism, primary bone marrow disorders, and certain drugs, including antimetabolites (zidovudine, azathioprine, methotrexate). Generation of thymidylate is mediated by TS; inhibition of the same enzyme is responsible for the cytotoxic activity of 5-FU. In the third level, MCV increase caused by capecitabine showing its effect by transforming to 5-FU may also be due to the inhibition of TS in erythroid precursor cells as well as the tumor cells [7]. Red blood cells enter the circulation from the bone marrow as reticulocytes, which are macrocytic with an MCV ranging from 100 to 125 fL. As a result , excessive numbers of reticulocytes in the peripheral blood can also lead to an overall increase in MCV. Absence of macrocytosis due to 5-FU can be due to its short duration of action because capecitabine is both administered for a long period of time and blood concentration remains constantly elevated and is completely absorbed from the gastrointestinal system after intake.

Although the exact reason for not seeing macrocytosis in every patient receiving capecitabine is not known, it can be associated with TS polymorphism in erythroid precursor cells because there are reports that TS polymorphism in peripheral blood cells may be used as a surrogate for intratu-

moral TS and TS polymorphism is responsible for both response to and toxicity from 5-FU [23,24]. Because our study was retrospective, we could not study TS polymorphism. Although this study is limited by its retrospective nature, the current preliminary results included the largest number of capecitabine-treated mCRC with a blood count analysis for macrocytosis presented to date. Evaluation of MCV levels after capecitabine treatment may be important for predicting the clinical course and survival. In our study, MCV increase was a significant independent prognostic factor. We believe that prospective studies (on the basis of this preliminary study) examining TS polymorphism in patients with MCV increase can shed light on the unknown points of this subject.

In summary, althouth our understanding on the etiology of capecitabine-related macrocytosis remains limited, it is likely reflective of deranged DNA synthesis and, as a result, of increased prevalence of immature erythrocyte precursors in circulation. The occurrence of MCV increase with capecitabine treatment does not require discontinuation of treatment and does not appear to impact toxicity. On the contrary, capecitabine-related macrocytosis might be used as a predictive marker of treatment response. Our results support this hypothesis. In addition, we showed that MCV increase can be a predictor of improved PFS and OS which are natural results of treatment response in patients with mCRC.

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