RESEARCH ARTICLE

Haematologic Parameters in Metastatic Colorectal Cancer Patients Treated with Capecitabine Combination Therapy

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Abstract

Background: The standard treatment in the metastatic colorectal cancer consists of 5-FU based infusional regimens. However, with oral fluoropyrimidines, equal tumor responses may be obtained. Capecitabine causes macrocytosis of the cells by inhibition of DNA synthesis. In this context, a relationship was found between mean corpuscular volume (MCV) and response to therapy in breast cancer patients treated with Capecitabine, but whether this relationship also pertains in colorectal cancer has not been established. Materials and Methods: A total of 102 metastatic colorectal cancer patients treated with a oxaliplatin (XELOX)±Bevacizumab combination were retrospectively evaluated. Patients were randomized into three groups. Hematological parameters (MCV, MPV, PCT, PLT, NLR) were recorded retrospectively, before treatment and after 3 cycles of chemotherapy. Results: After three cycles of therapy, 20 (19.6%) patients had progressive disease (PD), 41 (40.1%) had stable disease (SD), and 41 (40.1%) demonstrated a partial response (PR). In 62 (60.7%) treatment was with capesitabin plus XELOX therapy, and in 40 (39.2%) it was XELOX-Bevacizumab combination therapy. There was no difference among three groups before the treatment in terms of MCV, MPV, PCT, PLT, and NLR. MCV showed significant increase in chemotherapy response groups (PR and SD). In addition, a significant decrease was observed for platelet count in chemotherapy response groups. While NLR decrease was seen in only a PR group, PCT decrease was observed in all three groups. PCT and PLT values were higher in patients receiving Bevacizumab. Conclusions: PLT, PCT, MPV, and NLR values were decreased due to Capecitabine-based chemotherapy, however MCV was increased. PCT and PLT values were higher in patients who received Bevacizumab than those who did not. MCV, PLT, and NLR can be considered as important factors in predicting response to colorectal carcinoma treatment.

Keywords: Colorectal cancer - chemotherapy response - MCV - PLT - NLR

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Introduction

Colorectal cancer is the third most common cause of deaths from cancer worldwide (Jemal et al., 2011). Capecitabine is an oral flouroprimidin mainly used in various cancers, including colorectal cancer. It is metabolized to its active form 5-fluoruracil (5-FU) by the enzyme thymidine phosphorylase, which exists in higher concentrations in tumor tissue and liver than in normal tissues. 5-FU has been associated with megaloblastic changes, likely secondary to DNA-directed toxicity (Grem et al., 1993). There has been some studies showing the effect of MCV increase on prognosis in patients with metastatic breast cancer treated with Capecitabine (Arslan et al., 2011).

It has been demonstrated that various human and animal tumor cells have the ability to aggregate platelets and that this capacity correlates with the tumor's metastatic potential (Jurasz et al., 2002; Alonso-Escolano et al., 2004). It is well-established that platelets carry a multitude of angiogenesis regulatory proteins in their granules, and the normal ranges of angiogenesis regulators have been characterized in human platelets and in the platelets of patients with malignancy (Peterson et al., 2010).

Recently, the contribution of host inflammatory reactions to cancer development has been reported. Immunocompetent lymphocytes and neutrophils play a crucial role in the systemic inflammatory response. The neutrophil-lymphocyte ratio (NLR) has been used not only as a marker of inflammation, but also as a prognostic index for various common solid tumors such as gastric cancer, breast carcinoma, colorectal carcinoma, nasopharyngeal cancer and malignant melanoma (Roxburgh et al., 2009; Noh et al., 2013; Mallappa et al., 2013).

Bevacizumab is a humanized anti-VEGFA monoclonal antibody able to produce clinical benefit in metastatic

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colorectal cancer patients when combined to chemotherapy. The association between Bevacizumab, which is demonstrated to increase the risk of thromboemboli (Hapaniet al., 2011). PCT and MPV are important parameters showing platelet functions, and MPV, PLT and PCT declines was shown in earlier studies in patients with metastatic colorectal cancer treated with Bevacizumab (Mutlu et al., 2012).

The aim of this study was to perform a comprehensive analysis of routinely measured systemic inflammatory and hematological parameters (NLR, PLT, MCV, MPV, and PCT) and are these markers show response to chemotherapy, in patients with metastatic colorectal cancer treated with fist-line XELOX±Bevacizumab.

Materials and Methods

This study included 102 metastatic CRC patients. The patients were enrolled in the study between 2004 and 2011. A total of 102 patients were evaluated that treated with XELOX or XELOX+Bevacizumab protocols. Patients' responses to chemotherapy were evaluated by RECIST criteria and randomized into the three different groups; progressive disease (PD), stable disease (SD) and partial response group (PR). Hematological values (MCV, PLT, MPV, PCT, PLT, NLR) of the patients were recorded retrospectively before treatment and after 3 cycle treatment. The Regional Scientific Ethical Committee approved the study. Written informed consent was obtained from each patient before enrolment in the study.

Chemotherapy

All patients received XELOX±Bevacizumab combination chemotherapy as first line treatment for metastatic disease, which consisted of oxaliplatin 130 mg/m2on day 1 followed by oral capecitabine 2000 mg/m^2 on days 1-14 p.o. and Bevacizumab 7,5 mg/kg of a 21-day cycle. After the 3rd cycle of chemotherapy response was reevaluated clinically and radiologically by using CT scan of the thorax and abdomen according to RECIST criteria (Therasse et al., 2000, EORTC version 2000).

Statistics

Statistical analysis was performed using SPSS 18.0 package program. Kruskal-Wallis, Wilcoxon, 2-sample T test were used. p value <0.05 was considered statistically significant.

Results

The median age of patients was 60 years (range, 26-79) years. Twenty patients (19.6%) were in PD group, 41 (40.1%) patiens were in SD group, 41 (40.1) of them were in PR group after 3 cycle treatment. Two patients in PR group had complete response. Sixty-two patients (60.7%) treated with XELOX, while 40 (39.2%) patients had taken XELOX+Bevacizumab. Demographic characteristics of the patients are shown in Table-1. Thrombosis was observed in 11 (10.8%) patient under treatment. Thrombosis was observed 7 of the patients (6.8%) receiving Bevacizumab treatment. There was no difference among three groups

Table 1. Demographic Characteristics of the Patients

Demographic Characteristics		n	%
Sex	Male	52	51
	Female	50	49
Performance Score	PS0	58	56.9
	PS1	35	34.3
	PS2	9	8.8
Pathology	Adeno	94	92.2
	Signet-ring	3	2.9
	Mucinous	4	3.9
	Anaplastic	1	1
Tumor localization	Colon	71	69.6
	Rectum	31	30.4
Surgery	NO	27	26.5
	YES	75	73.5
Adjuvant Chemotherapy	NO	85	83.3
	YES	17	16.7
Adjuvant Radiotherapy	NO	92	90.2
	YES	10	9.8
Metastasis Number	Single	77	75.5
	Multiple	25	24.5
Metastasis Localization	Liver only	76	74.5
	Lung only	6	5.9
	Liver+Lung	8	7.8
	Peritoneum	8	7.8
	Other	4	3.9

Table 2. Changes in Hematological Parameters According to Chemotherapy Response

Patient Response	Baseline level	After 3rd cycle	p
Partial Response			
MCV (fl)	83.4±6.98	88.72±8.38	<0.001
PLT(10^3/μL)	359±171	239±239	0.001
PCT (%)	0.33±0.16	0.20±0.08	<0.001
MPV(fl)	9.25±1.01	9.1±1.01	0.381
NLR (10^3/μL)	3.89±3.1	2.45±2.45	0.02
Stable Disease			
MCV(fl)	82.8±11.8	88.57±7.7	0.003
PLT(10^3/μL)	329±119	234±148	<0.001
PCT (%)	0.29±0.1	0.20 ±0.1	<0.001
MPV (fl)	9.33±1.22	8.85±1.13	0.01
NLR (10^3/μL)	3.96±3	3.21±3	0.3
Progressive Disease			
MCV (fl)	82.3±8.9	84.9±6.1	0.089
PLT (10^3/μL)	393±160	309±149	0.079
PCT (%)	0.35±0.13	0.26±0.11	0.009
MPV (fl)	9.73±1.1	9.16±1.1	0.030
NLR (10^3/μL)	3.7±3	2.86±1.63	0.213

before the treatment in terms of MCV, MPV, PCT, PLT, and NLR (p=0.91, p=0.21, p=0.22, p=0.36, p=0.95 respectively). However, when the same parameters were re-evaluated after three cycles of chemotherapy, there was no statistically significant difference among the groups. Assessment of patients within the group (PD, SD and PR) and variation of parameters is shown in Table-2. When analyzing the patients who were received XELOX and XELOX-Bevacizumab in pre-treatment status they did not differ in terms of hematological parameters at the time of diagnosis, but higher values were found in terms of the values of the PCT and PLT in patients receiving Bevacizumab; PCT (0.19 *vs* 0.25; p=0.009) and PLT (206 *vs* 317; p=0.001) after three cycles of chemotherapy. Similarly thrombosis were more common in patients who

received Bevacizumab therapy (7 *vs* 4 pts p=0.07).

Discussion

To the best of our knowledge, this is the first study to describe the use of NLR, PLT, MPV, PCT, and MCV in metastatic colorectal cancer patients receiving first-line palliative chemotherapy in terms of providing useful information regarding prognostication. This study also reports the investigation of the utility of NLR, MCV and other hematological parameters during the course of chemotherapy, in particular the normalization of NLR and MCV, to predict early responses to treatment. The NLR and MCV can be calculated from the data that are already routinely available. It does not require any additional expenditure. Moreover, hematologic markers are much cheaper and faster laboratory parameters, which can be measured than conventional tumor markers. The NLR and MCV can be used to routinely evaluate blood chemistry parameters for outpatients because of their lower cost and greater convenience in comparison with complex and expensive techniques.

The chemotherapy agent 5-FU, which has been used against cancer for about 40 years, acts in several ways, but principally as a thymidylate synthase (TS) inhibitor. Interrupting the action of this enzyme blocks synthesis of the pyrimidine thymidine, which is a nucleoside required for DNA replication. Whenever the formation of cell DNA from thymidylate is slowed down, the prolonged cell cycle allows excess synthesis of RNA and other cytoplasmic components including hemoglobin, leading to the increased size of red blood cells in megaloblastic anemia (Hoffbrand et al., 1972). This can be the result of severe deficiencies of vitamin B12 and folic acid, as well as Capecitabine treatment as a result of the inhibition of TS in erythroid precursor cells. The consistent finding of macrocytosis during Capecitabine treatment.

In a retrospective review on metastatic breast cancer patients receiving standard dose oral Capecitabine therapy, MCV increased in a dose-dependent and time-dependent manner during chemotherapy, with 57% of study patients developing macrocytosis while on Capecitabine (Karvellas et al., 2004). Wenzel et al. (2003) observed a statistically significant increase of MCV in advanced cancer patients receiving Capecitabine (2500 mg/m^2/day for 14 days every 21 days) either as monotherapy or in combination with other antineoplastic agents within 9 weeks which was probably due to the 5-FU-induced TS inhibition in erythroid precursor cells. Wenzel et al. showed that higher MCV values were seen in patients with tumor remission or stable disease rather than in patients with tumor progression, but the difference was not statistically significant (Wenzel et al., 2003). In contrast to the literature, in our study, when analyzing the intra-group of patients, MCV values were increased from baseline in all three groups. However, this increase was statistically significant PR and SD groups. Significant increase in MCV in predicting response to Capecitabine-based chemotherapy seems to be an important parameter.

Bevacizumab is a humanized monoclonal antibody directed against VEGF-A. There are no data on the possible role of Bevacizumab on the development of macrocytosis. In our study, there was no significant difference in terms of MCV between in patients treated with Bevacizumab or without.

Chronic inflammation can be caused by infection, malignant tumors, autoimmune disease or other pathologies and results in the infiltration of inflammatory cells. Inflammation is thought to contribute to the development and progression of various cancers (Altinoz et al., 2004; Biarc et al., 2004). It is only been in the past decade, however, that the complexities of the tumor inflammatory microenvironment and the host's response to tumor induced inflammatory pathways have begun to be understood, resulting in an improved ability to prevent and treat malignancy. The new paradigm in tumor immunology states that the tumor microenvironment can educate and control invading leukocytes to promote angiogenesis, viability, motility, and invasion (Balkwill et al., 2001; Lin et al., 2004).

Elevated NLR have also been repeatedly demonstrated as a significantly prognostic factor for some other types of cancer (Noh et al., 2013; Pichler et al., 2013; Shibutani et al., 2013). Patients with elevated NLR have a relative lymphocytopenia and, as a result, may exhibit a poorer lymphocyte-mediated immune response to malignancy; thereby worsening their prognosis. Walsh et al. (2005) was the first to report that preoperative elevated NLR was correlated with overall and cancer-specific survival in colorectal cancer. In this study compared to baseline, NLR values decreased in all three chemotherapy received groups. However, significant reduction was seen in terms of NLR in PR group. When assessing the patients who were received XELOX and XELOX-Bevacizumab in terms of NLR at the time of diagnosis and at the end of the third cycle of chemotherapy, NLR values did not differ.

Platelets are best known for their role in hemostasis and thrombosis. Platelets have additional roles in wound healing, inflammation and angiogenesis. Studies have shown that platelet count can be a prognostic factor; with patients presenting with thrombocytosis having a poor survival in a variety of cancers (Monreal et al., 1998 ; Sun et al., 1979). Italiano et al. showed that platelets store angiogenic factors in granules and that these granules can be differentially released in the presence of the thrombin agonists (Italiano et al., 2008). Mean platelet volume (MPV) and platecrit (PCT) are crucial indicators, which are associated with platelets functions. MPV level was considerably higher in pre-operative gastric cancer patients compared to healthy subjects (Kılınçalp et al., 2013) .

In this study; when analyzing the pretreatment status, there was no difference in terms of MPV, PCT and PLT among three groups. However after three cycles, borderline significance was found in terms of PCT among the groups (statistical higher in the group PD). MPV, PCT, and PLT values were decreased compared to pre-treatment levels in all three groups. However, decrease in the PLT value was only in PR and SD groups. The significant PCT decline was seen in all three groups, but MPV decline was seen in SD and PD groups.

When assessing the patients who were received

XELOX and XELOX-Bevacizumab in pre-treatment status and after three cycle of chemotherapy, they did not differ in terms of MCV, MPV, PCT, PLT and NLR at the time of diagnosis. However, after three cycles of treatment, PCT and PLT values were higher in patients receiving Bevacizumab, which has been reported to be associated with delayed wound healing, gastrointestinal perforation, hemorrahage, venous and arterial thromboembolism, hypertension and proteinuria (Gordon et al., 2005). In addition, arterial thrombosis has been observed to be increased in patients with metastatic colon cancer using Bevacizumab (Scappaticci et al., 2007). Similarly, our study showed a higher incidence of thrombosis in patients receiving Bevacizumab (7 *vs* 4 pts) (p=0.07). Contrary to Mutlu et al.(Mutlu et al., 2012), our study showed that PCT, PLT and MPV decline does not depend on the effect of Bevacizumab, but due to the chemotherapy.

In conclusion, we found that pretreatment routine hematological parameters including NLR, MCV, and PLT were correlated with prognosis in patients with metastatic colorectal cancer who had been treated with XELOX±Bevacizumab. Although this study was a retrospective analysis and a single-center study, it indicates the potential usefulness of a new predictor of response to chemotherapy. The low cost and easy accessibility and reproducibility of a full blood count are other features promoting its use in clinical practice. To confirm these findings, larger, prospective, randomized studies are required in future.

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