RESEARCH ARTICLE

Mean Platelet Volume as a Prognostic Marker in Metastatic Colorectal Cancer Patients Treated with Bevacizumab-Combined Chemotherapy

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Abstract

Background: Recent studies have revealed a prognostic impact of the MPV (mean platelet volume)/platelet count ratio in terms of survival in advanced non-small cell lung cancer. However, there has been no direct analysis of the survival impact of MPV in patients with mCRC. The aim of the study is to evaluate the pretreatment MPV of patients with metastatic and non-metastatic colorectal cancer (non-mCRC) and also the prognostic significance of pretreatment MPV to progression in mCRC patients treated with bevacizumab-combined chemotherapy. Materials and Methods: Fifty-three metastatic and ninety-five non-metastatic colorectal cancer patients were included into the study. Data on sex, age, lymph node status, MPV, platelet and platecrit (PCT) levels were obtained retrospectively from the patient medical records. Results: The MPV was significantly higher in the patients with mCRC compared to those with non-mCRC (7.895±1.060 versus 7.322±1.136, p=0.013). The benefit of bevacizumab on PFS was significantly greater among the patients with low MPV than those with high MPV. The hazard ratio (HR) of disease progression was 0.41 (95%CI, 0.174-0.986; p=0.04). In conclusion, despite the retrospective design and small sample size, MPV can be considered a prognostic factor for mCRC patients treated with bevacizumab-combined chemotherapy.

Keywords: Colorectal cancer - MPV - bevacizumab - platelet - prognosis

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Introduction

Platelets play an important role in inflammation that is a critical component of tumor progression. They secrete proinflammatory and growth factors such as platelet activated factor (PAF), vascular endothelial growth factor (VEGF), platelet derivate growth factor (PDGF), and thromboxane A2 (TXA2) (Matowicka et al., 2013). The VEGF family includes six members: VEGF-A, -B, -C, -D, -E and placental growth factor. VEGF-A is the most important member that regulates angiogenesis by increasing vascular permeability and accelerating the branching and formation of new blood vessels in the tumor. It has been shown to promote hematogenous tumor spread. Angiogenesis and increased blood vessel density in the primary tumor are often correlated with poor prognosis and increased relapse rate (Cai et al., 2013).

In Europe, colorectal cancer (CRC) is the second most common cancer that leads to death, remains a significant health problem (Jemal et al., 2010). In the last decade, a combination chemotherapy regimen with targeted therapy has become standard treatment of unresectable metastatic CRC (mCRC) and improved median survival to over two years (Van Custen et al., 2009). Biomarkers predictive of favorable response to targeted therapy are playing an increasingly important role in personalized mCRC (Amado et al., 2008). KRAS and BRAF mutations are accepted as a negative predictive factor in mCRC patients treated with anti-EGFR agents, such as cetuximab and panitumumab. Bevacizumab is recombinant humanized monoclonal antibody that neutralizes VEGF-A, inhibits tumor angiogenesis, has been widely used for the treatment of mCRC, and prolongs survival when it is combined with chemotherapy regimens. At the time, there are currently no biomarkers avaible to predict the efficacy of anti-VEGF therapy.

Mean platelet volume (MPV) is platelet volume index and indicator of thrombocyte volume (Mutlu et al., 2013). Recent studies revealed that the prognostic and diagnostic impact of the MPV/platelet ratio, platelet/lymphocyte ratio and neutrophil/lymphocyte ratio in various cancers, including colon cancer, lung cancer (Unal et al., 2013; Dirican et al., 2014; Inagaki et al., 2014; Kemal et al., 2014; Ozdemir et al., 2014;).

However, there has been no direct analysis of the survival impact of MPV in patients with mCRC. The

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aim of the study is to evaluate the pretreatment MPV of patients with metastatic and non-metastatic colorectal cancer (non-mCRC) and also the prognostic significance of pretreatment MPV to progression in mCRC patients who have been treated with bevacizumab-combined chemotherapy.

Materials and Methods

148 patients with CRC who were admitted to the Gata Haydarpasa Training Hospital between 2004 and 2014 were enrolled in this retrospective study. Of the patients, 53 were metastatic and 95 were non-metastatic. Patients who were at least 18 years old with histologically confirmed CRC; with no previous chemotherapy history for non-mCRC patients and metastatic disease treated with first-line chemotherapy combined with bevacizumab therapy were included. Patients were excluded if they had a history of any other cancer, autoimmune diseases, vascular thromboembolism, and heart, hepatic failure.

Data on sex, age, lymph node status, MPV, platelet and platecrit (PCT) levels were obtained retrospectively from the patient's medical records. Automated blood counter (Coluter Gen-S, Minnesota, MN, USA) had been used for complete blood count (CBC) analysis. MPV values were documented at diagnosis before treatment. SPSS software was used to analyze the data. The mCRC patients were seperated into two groups according to mean value of MPV (low: <7.89 or high: ≥7.89). As the MPV was not normally distributed, shown by Kolmogorov-Smirnov test the compression of MPV between metastatic and non-metastatic CRC was performed by Mann-Whitney U test. The primary objective of this study was to evaluate the prognostic value of MPV on PFS for mCRC patients treated with first-line chemotherapy plus bevacizumab. PFS was defined as the time from the beginning of the treatment until the first observation of radiologic progression or death from any cause. Kaplan-Meier method was used for estimation of survivals; differences in survival were evaluated by the log-rank statistics. A P value of < 0.05 was considered to be statistically significant. A local Ethical Committee approved our study.

Results

We studied 148 patients with CRC: 53 (27 male and 26 female) metastatic and 95 (55 male 40 female) non-metastatic. The baseline characteristics and platelet indices are summarized in Table 1. The MPV was significantly higher in the patients with mCRC than those with non-mCRC (7.895±1.060 versus 7.322±1.136, p=0.013). However, there was no statistically significant difference in platelet counts between patients with non-mCRC versus patients with mCRC (302.9±96.5 versus 320.9±108.9, p=0.3). Similarly, there was no statistically significant difference in PCT patients with non-mCRC versus patients with mCRC (0.236±0.081 versus 0.217±0.061, p=0.149).

Among patients with mCRC, 43 patients had been treated bevacizumab-combined chemotherapy. Median PFS for all patients was 320 days. At the end of the observation, 24 (44%) patients had progressive disease. Among patients with mCRC, the median PFS was 353 days in the group with low MPV and was 273 days in the group with high MPV (Table 2). The benefit of

Table 1. Baseline Characteristics and Platelet Indices among the Metastatic and Non-metastatic CRC Patients

		non-mCRC (n=95)	mCRC (n=53)	p value
Age	Mean	58.7	66.4	
	Std. D	8.4	9.1	
	Min	29	41	
	Max	81	79	
Sex	Male	55	27	
	Female	40	26	
MPV	Mean	7.322	7.895	0.013
	Std. D	1.136	1.06	0.013
	Min	4.3	6.1	
	Max	9.9	10.8	
Platelet	Mean	302.9	320.9	0.3
	Std. D	96.5	108.9	
	Min	126	153	
	Max	580	707	
Platecrit	Mean	0.236	0.217	0.149
	Std. D	0.081	0.061	
	Min	0.1	0.11	
	Max	0.58	0.38	
	I	18	3	
Grade	II-III	66	30	
	III	11	20	
Lymph Node	Positive	41	0	
	Negative	54	0	
	Metastatic	0	53	
Stage	I	2	0	
	II	51	0	
	III	42	0	
	IV	0	53	

Table 2. Treatment Details and PFS Times of mCRC According to MPV

		mCRC	
Chemotherapy Type	Other	10	
	Folfiri-B	27	
	Folfox-B	1	
	Ifl-B	15	
	Low	mCRC (p value)	High
Number	19		24
Progression	8		16
PFS (median)	353±138	p=0.04	273±58

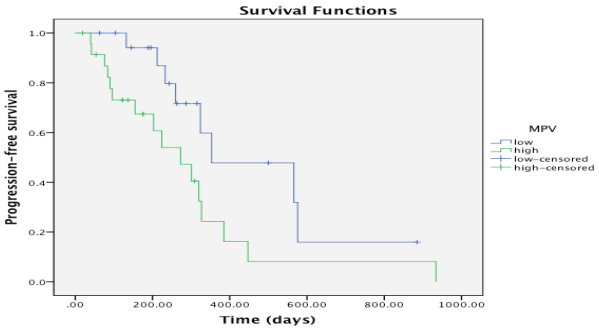

Figure 1. Progression-free Survival Curves in mCRC Patients According to MPV Levels (p=0.04)

bevacizumab on PFS was significantly greater among the patients with low MPV than patients with high MPV (Figure 1). The hazard ratio (HR) of disease progression was 0.41 (95% CI, 0.174-0.986; p=0.04).

Discussion

Chemotherapy with targeted therapy is the first treatment option for unresectable mCRC patients (Hurwitz et al., 2004; Kabbinavar et al., 2005). Bevacizumab has shown efficacy in both previously treated and untreated metastatic CRC (Giantonnio et al., 2007). To date, a few specific predictive biomarkers for bevacizumab treatment have been identified. Bar et al have been found that high total lactate dehydrogenase isoenzyme were associated with poor prognosis (Bar et al., 2014). Aykan et al showed that high body mass index among mCRC patients treated with bevacizumab are associated with shorter time to progression (Aykan et al., 2013). Cai et al reported that bevacizumab-induced hypertension might represent a prognostic factor in patients with mCRC (Cai et al., 2013).

Platelets play important role in pathophysiology of tumor angiogenesis by transporting VEGF, which is the target for anti-angiogenic agents (Oge et al., 2013). MPV is a parameter of platelet size and can reflect changes in the rate of platelet production. Previous studies have demonstrated that the MPV was higher in patients with gastric cancer than in control patients and also MPV/PC (platelet count) ratio was significantly increased in the hepatocellular carcinoma patients (Cho et al., 2013; Kilincalp et al., 2013). In addition, Oge et al. (2013) showed that MPV was significantly higher in endometrial cancer patients than the control group. Our data showed statistically significant differences in MPV values between mCRC and non-mCRC, this may be explained with the increased inflammation and increased platelet activation in the metastatic disease.

To date, MPV have been not evaluated in mCRC patients who treated with bevacizumab-combined chemotherapy. Patients with mCRC who had been treated with bevacizumab-combined chemotherapy were separated into two groups according to mean value of MPV. Median PFS time for patients with high MPV were statistically shorter than patients with low MPV. It has been known that larger platelets are more trombogenic and active than smaller platelet. We can speculate that increased platelet activity, which can be evaluated by measuring MPV, may have a detrimental effect on Bevacizumab therapy.

In conclusion, despite the retrospective design and small sample size, MPV can be considered a predictive factor for mCRC patients treated with bevacizumab-combined chemotherapy. Further prospective studies on larger of patients are needed to determine the effect of MPV on bevacizumab-combined chemotherapy.

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