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Research Article

The Relationship Between Bevacizumab Treatment and Platelet, Mean Platelet Volume and Thromboembolic Events in Patients with Metastatic Colorectal Cancer

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Abstract

Objectives: Colorectal cancer (CRC), is one of the leading causes of mortality worldwide and is the second most common cancer in developed countries. Bevacizumab, a recombinant humanized monoclonal antibody to vascular endothelial growth factor has been approved for use in combination chemotherapy for the first or second-line treatment of patients with metastatic colorectal cancer. The risk of arterial thromboembolism was found to be higher in the patients received combination treatment with bevacizumab. Mean platelet volume is a parameter that measures the platelet size and is defined as a marker of platelet reactivity.

Methods: A total of 108 patients from medical oncology department of Acibadem Kayseri Hospital with metastatic colorectal cancer and receiving first line combination treatment with bevacizumab were included in this study. Age, gender, comorbidity status, body mass index, smoking status and the type of chemotherapy combination were also enrolled.

Results: At the 3rd month of the treatment, mean platelet volume levels were found to be increased in the total patient group from 8.98±0.16 to 9.28±0.14 and this was statistically significant ($p<0.0001$). Also there were significant increases in mean platelet volume values in the patients with normal body mass index, non-smokers and the patients who did not have any comorbidity. Platelet values did not change in any of the subgroups except for the patients over 65 years of age.

Conclusion: Based on the results of our study, we think that bevacizumab induced thrombosis can be achieved through MPV increase. The fact that MPV increases especially in the patients without comorbidity, in non-smokers and in normal-weight patients, suggest that bevacizumab leads to a condition that causes MPV increase regardless of these factors and so special attention should be paid to MPV values in the follow-up of the patients receiving chemotherapy protocols containing bevacizumab. Due to the number of physiological variables affecting the platelet size and poor standardization of mean platelet volume measurement, properly designed clinical studies -with more personalized reference ranges and better methodological standardization- are needed to make it a reliable parameter for differential diagnosis and prognostic identification of thrombosis in the metastatic colorectal cancer patients receiving bevacizumab combination treatment.

Keywords: Bevacizumab, colorectal cancer, mean platelet volume, thromboembolic events

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Colorectal cancer (CRC), is one of the leading causes of mortality worldwide and is the second most common cancer in developed countries.[1] Predominantly, it is a disease of the elderly and in the United States, more than two thirds (68%) of the CRC patients are diagnosed over the age of 65 and the median age at diagnosis is 72 years.[2] The

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National Comprehensive Cancer Network, an alliance of 19 leading cancer centers in the United States, recommends chemotherapy in all patients with metastatic CRC (mCRC) except those with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 3 or 4, in whom best supportive care is recommended.[3]

Bevacizumab, a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF) has been approved for use in combination with intravenous 5-FU–based chemotherapy for the first- or second-line treatment of patients with mCRC, at a dose of 5 mg/kg or 10 mg/kg every 2 weeks until disease progression.[4] Besides its effectiveness in colon cancer,[5] also it has beeen shown to be effective in ovarian cancer,[6] brain tumors,[7] renal cancer,[8] breast cancer[9] and lung cancer[10, 11] Bevacizumab has also some side effects such as hemorrhage, delay in wound healing, gastrointestinal system perforation, proteinuria, hypertension, and thromboembolic events, reported in the literature.[12] Thrombosis has been well investigated and the risk of arterial thromboembolism was found to be higher in the patients received combination treatment with bevacizumab and chemotherapy, compared with chemotherapy alone.[13]

Venous thromboembolism (VTE) is a common complication in patients with cancer and the patients with cancer who develop symptomatic VTE during chemotherapy are at a greater risk of early mortality than those without VTE.[14] Deep-vein thrombosis is seen approximately in 30% of colorectal cancer surgery patients without thromboembolic prophylaxis.[15]

Mean platelet volume (MPV) is a parameter that measures the platelet (PLT) size and is defined as a marker of PLT reactivity.[16] Compared to normal sized PLTs, larger PLTs were found to be hemostatically more reactive.[17]

Previous studies showed the relation of increased MPV and thromboembolism in many diseases such as diabetes mellitus,[18] myocardial infarction,[19] cerebrovascular thromboembolism[20] and also in smokers.[21]

Similarly to increased MPV, also bevacizumab treatment increases the risk of thromboembolic events. Based on this similarity, we investigated the relationship between bevacizumab treatment and PLT, MPV and thromboembolic events in patients with mCRC. The aim of our study was to determine whether combination therapies including bevacizumab had an effect on PLT and/or MPV, or not.

Methods

A total of 108 patients from medical oncology department of Acibadem Kayseri Hospital with mCRC and receiving first line combination treatment with bevacizumab were included in this study. The study was approved by the Acibadem University Ethics Committee. Age, gender, comorbidity status, body mass index (BMI), smoking status and the type of chemotherapy combination were also enrolled. Additionally, subgroup analyses were performed according to gender and age (younger and older than 65 years). The comorbid diseases included hypertension, diabetes mellitus and coronary artery disease. A value between 18.5-25 for BMI was considered normal and a value greater than 25 as overweight. PLT and MPV levels were recorded using Statistical Package for the Social Sciences 22.0 (SPSS22.0) statistical software at the time of bevacizumab initiation and at the third month of the treatment. Frequency analyses and paired sample t test were performed and the p value <0.05 was considered statistically significant.

Table 1. The characteristics of patients

Parameters	n	%	Median (years)
Total	108		–
Age			62 (27-80)
Male	65	60.2	
Female	43	39.8	
Comorbidity status			
With comorbidity	31	28.7	–
Without comorbidity	77	71.3	–
BMI			
Normal	54	50.0	–
Overweight	54	50.0	–
Smoking status			
Smoker	53	52.5	–
Non-smoker	48	47.5	–
Combination treatment			
FOLFIRI+Bevacizumab	63	58.3	–
Folfox/xelox+Bevacizumab	45	41.7	–

BMI: Body mass index; FOLFIRI: Folinic acid+ fluorouracil+ irinotecan; Folfox/xelox: Folinic acid+ fluorouracil+oxaliplatin/capecitabin+ oxaliplatin.

Results

The median age of the 108 patients was 62 (27-80). 43 (39.8%) of the patients were females and 65 (60.2%)were males. 31 (28.7%) of the patients had comorbidities, while the remaining 77 (71.3%) had no comorbidity. Half of the patients, 54 (50.0%) were in normal weight and the other half 54 (50.0%) were overweight. 53 (52.5%) were smokers and 48 (47.5%) were non-smokers.

Regarding the type of therapy, 63 (58.3%) of the patients received folinic acid–fluorouracil–irinotecan (FOLFIRI)+bevacizumab combination and 45 (41.7%) of the patients received folinic acid-fluorouracil- oxaliplatin (FOLFOX)/capecitabin+ oxaliplatin (xelox)+bevacizumab combination. The characteristics of patients were presented in Table 1.

At the 3rd month of the treatment, MPV levels were found to be increased in the total patient group from 8.98±0.16 to 9.28±0.14 and this was statistically significant (p<0.0001). But in the subgroup analyses, MPV levels did not change among the males, females and the patients younger than 65 years of age or over 65 years of age (p values were 0.058, 0.130, 0.148 and 0.096 respectively). While there were significant increases in MPV values in the patients with normal BMI, non-smokers and the patients who did not have any comorbidity (p values were 0.004, 0.001 and <0.0001 respectively); we did not observe any changes in MPV values in the overweight patients, smokers and the patients with comorbidities (p values were 0.068, 0.127 and 0.202 respectively).

Examination of the patients for PLT showed that the PLT values did not change in any of the subgroups except for the patients over 65 years of age. In this group, PLT levels were found to be decreased from 278.030±19.361 to 199.060±16.811 at the 3rd month of the treatment and this was statistically significant (p value: 0.009) (Table 2).

In our study, arterial thrombotic events (ATEs) occurred in 5 (4.6%) patients. One patient had acute myocardial infarction, one pulmonary embolism, one occlusion in the extremity and the other two patients had serebrovascular diseases. Venous thromboembolic events (VTEs) occurred in 9 (8.3%) patients. There was not a sufficient number of patients who will explain statistically whether there is a significant difference in terms of MPV values between those with and without arterial or venous thrombosis, therefore, no evaluation has been made in this direction.

Table 2. MPV and PLT values

Parameters	Mean value prior to the treatment	Third month mean value	p
Platelet 10^3/ml	329.550±20.186	216.420±8.785	0.212
Male	324.810±32.216	211.930±10.963	0.121
Female	310.914±16.602	22.710±14.557	0.241
Age<65	358.780±29.177	225.620±9.970	0.248
Age >65	278.030±19.361	199.060±16.811	**0.009**
BMI normal	340.710±38.002	221.980±13.302	0.077
BMI overweight	318.600±14.830	210.960±11.567	0.287
Smokers	379.920±37.882	238.940±13.227	0.256
Non-smokers	290.480±14.726	196.020±12.371	0.088
With comorbidity	334.830±23.374	210.930±17.416	0.273
Without comorbidity	327.540±26 507	218.520±10.221	0.118
MPV	8.98±0.16	9.28±0.14	**<0.0001**
Male	8.96±0.21	9.12±0.18	0.058
Female	9.02±0.25	9.02±0.23	0.130
Age <65	8.59±0.21	8.97±0.19	0.148
Age >65	9.67±0.20	9.29±0.20	0.096
BMI normal	8.92±0.24	9.14±0.21	**0.004**
BMI overweight	9.05±0.21	9.02±0.19	0.068
Smokers	8.54±0.23	8.85±0.21	0.127
Non-smokers	9.29±0.21	9.40±0.19	**0.001**
With comorbidity	9.01±0.28	9.02±0.28	0.202
Without comorbidity	8.97±0.19	9.10±0.17	**<0.0001**

MPV: Mean platelet volume; PLT: Platelet; BMI: Body mass index.

Discussion

Cancer is a disease with an increased risk of thrombosis and is one of the two leading reasons of cancer mortality along with infection.[22] Three mechanisms responsible for prothrombotic process have been defined in patients with malignancy: reactivity of platelets, inactivation of fibrinolytic system and the elevation of procoagulation factors secreted from the cancer cells.[23] Thrombosis formation is triggered by these 3 mechanisms in the presence of predisposing factors such as radiotherapy, chemotherapy, surgical intervention and venous stasis.[24]

Bevacizumab is a recombinant humanized monoclonal anti-body to VEGF approved for use in the combination treatment of mCRC and has been found to increase arterial thrombotic events in several randomized controlled trials.[10, 25, 26] A study showed that bevacizumab increases the risk of ATEs especially in the patients over 65 years of age with poorer performance status and also in patints with a history of previous ATEs.[27] In previous meta-analyses, the incidence of ATEs was reported to be between 0.6% and 5.6%[13, 28–30] and the incidence of VTEs was reported to be between 6.8% and 19.9%[31] among patients with different cancer types treated with bevacizumab. For CRC, the incidence of ATEs was reported to be between 0.5% and 8.5%,[13, 28–30] and the incidence of VTEs was reported to be between 16.1% and 22.6%.[31]

In a meta-analysis by Alahmari KA, a total of 13.185 bevacizumab received patients with CRC from 22 randomized controlled trials were reported to have a significiant increase (>33%) for overall thromboembolic events and the use of bevacizumab led to an increase of 24% for VTEs and 62% for ATEs.[32]

Although several theories have been proposed, the exact mechanism of bevacizumab induced thrombosis is still unknown. One theory suggests that the inhibition of the physiological anti-inflammatory effect of VEGF causes vascular inflammation and eventually thrombus development. In addition, inhibition of VEGF increases blood viscosity and platelet aggregation by decreasing nitric oxide and prostacycline production.[28, 29] According to another theory, bevacizumab produces toxic substances that inter-

act with malignant cells, which increase blood clotting.[31] Some researchers have suggested that the anti-VEGF activity of bevacizumab is related to the damage of endothelial walls of blood vessels and the reveal of subendothelial lipids by causing thrombosis formulation.[30, 31]

MPV is an indicator of platelet size and can bu used as an index of activated platelet.[33] Increased MPV levels are related with wide platelets which contain dense granules with more thromboxane A2 in the blood.[34] MPV was found to be useful for predicting the onset of venous thromboembolism and arterial thrombosis.[35]

Similarly to arterial thrombosis, many other acquired conditions such as diabetes,[36] obesity,[37] hypertension,[38] familial hypercholesterolemia,[39] obstructive sleep apnea syndrome[40] and chronic obstructive pulmonary disease,[41] have been found significantly associated with higher MPV.

Furthermore, there are studies suggesting that MPV can be used as a diagnosis marker in some cancers. Karaman et al. showed that he preoperative median MPV levels were significantly lower in patients with pancreatic neuroendocrine tumors than in patients with pancreatic adenocarcinomas (7.8 fL vs. 8.6; $p<0.014$).[42] Kilincalp S. et al. found that MPV level was significantly higher in pre-operative gastric cancer patients compared to healthy subjects (8.31 fL vs. 7.85; $p=0.007$)[43] and similarly Li JY et al. reported that elevated MPV was associated with presence of colon cancer.[14]

Another study showed that, the MPV values were significantly higher in the patients with mCRC compared to those with non-mCRC and the benefit of bevacizumab on progression free survival was significantly greater among the patients with low MPV than those with high MPV.[44]

The aim of our study was to determine whether combination therapies including bevacizumab had an effect on PLT and/or MPV, or not. In our study, the examination of the patients for PLT showed that the PLT values did not change in any of the subgroups except for the patients over 65 years of age and decreased in the patients over 65 years of age. PLT values were also shown to be decreased in another study.[45] The reason of this decrease only in the patients over 65 years of age can be explained by the more severe side effects of chemotherapy in elderly patients.

In our study, we also found that MPV levels increased significantly in the patients receiving combination therapies including bevacizumab at the third month of the treatment. Bevacizumab is known to increase the risk of ATEs however, there is not yet sufficient information on exactly which mechanisms it exerts this effect. Based on the results of our study, we think that this effect can be achieved through MPV increase. The fact that MPV increases especially in the patients without comorbidity, in non-smokers and in normal-weight patients, suggest that bevacizumab leads to a condition that causes MPV increase regardless of these factors.

For because bevacizumab treatment causes an increase in MPV values independently from other risk factors and MPV increase has a close relationship with thromboembolic events – one of the most important causes of morbidity and mortality in malignancy patients-, we think that special attention should be paid to MPV values in the follow-up of the patients receiving chemotherapy protocols containing bevacizumab. Patients with cancer who have a history of thrombosis or previously exposed to chemotherapy, who have undergone a major surgery or hospitalized, have a higher risk for thromboembolic events and should have taken thromboprophylaxis appropriately. But the 2019 updated guide of the American Clinical Oncology Association does not recommend prescribing thromboprophylaxis for outpatients. However, this guideline recommends low molecular weight heparin or low dose aspirin prophylaxis for thromboembolic events for patients with multiple myeloma who receive antiangionesis treatment such as thalidomid or lenalidomid.[46] After these results, the use of aspirin may be discussed for the prevention of thromboembolic events, without ignoring the risk of bleeding, in patients receiving bevacizumab therapy.

Conclusion

Due to the number of physiological variables affecting the platelet size and poor standardization of MPV measurement, properly designed clinical studies -with more personalized reference ranges and better methodological standardization-are needed to make MPV a reliable parameter for differential diagnosis and prognostic identification of thrombosis in the mCRC patients receiving bevacizumab combination treatment.

Disclosures

Ethics Committee Approval: The Ethics Committee of Acibadem University provided the ethics committee approval for this study (2020-01/32 - 09.01.2020).

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