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Original Research Article

Thrombocytosis as a predictor of thromboembolic complications in patients with malignant diseases

Branislava Jakovljević[1]*, Siniša Maksimović[2], Aleksandar Jakovljević[1], Darko Jović[1], Ljiljana Latinović[3], Jovan Ćulum[1], Nebojša Trkulja[4], Sanja Sibinčić[5], Amir Spahic[6]

[1]Hospital for Surgical and Internal Medicine, S. tetik, Banja Luka, Bosnia and Herzegovina
[2]General Hospital, Sveti Vračevi, Bijeljena, Bosnia and Herzegovina
[3]Department of Pathology, University Clinical Centre, Banja Luka, Bosnia and Herzegovina
[4]Department of Surgery, University Clinical Centre, Banja Luka, Bosnia and Herzegovina
[5]Health Institution, Medico-S, Banja Luka, Bosnia and Herzegovina
[6]Department of Pathology, Cantonal Hospital Travnik, Bosnia and Herzegovina

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***Correspondence:**
Dr. Branislava Jakovljević,
E-mail: onkologija.estetik@gmail.com

ABSTRACT

Background: To prove the frequency of thrombocytosis in patients with cancer, and the importance of anticoagulant therapy. Thrombocytosis represents an elevated platelet count of more than 350,000/mm^3 which is one of the risk factors for venous thromboembolism.
Methods: This study has analyzed 146 patients who were hospitalized at the Oncology Clinic of the University Clinical Centre, Banja Luka and the Day Oncology Hospital "S.tetik", Banja Luka in the period between 2009 and 2014. These were patients with breast tumor, gastrointestinal or gynecological malignancies. Thrombocytosis was detected in 38 patients in the moment of diagnosing. All examinees were analyzed by sex, age, primary site of tumor, presence of comorbidity, relevant laboratory analyses, clinical stage of the disease (metastatic or localized disease).
Results: In the observed sample of 146 patients, thrombocytosis was detected in 38 patients in the moment of diagnosing the disease (26%). Through the follow-up, DVT (deep venous thrombosis) was found in 13 patients (34.2%) and anticoagulant therapy was administered. Out of patients who were not on anticoagulant therapy because they had no thrombotic manifestations (25 patients, 65.8%), 2 ended up experiencing the development of a clinical presentation of massive pulmonary embolism with fatal outcome.
Conclusions: The occurrence of thromboembolism significantly increases morbidity and mortality, as well as the total cost of treating cancer patients. Regardless of the fact that cancer patients are at a high risk of thromboembolic events, thromboembolic prophylaxis has not been adopted as a standard therapeutic modality because of potential bleeding.

Keywords: Neoplasms, Risk factors, Thromboembolism

INTRODUCTION

The concept that platelets play key roles in cancer growth and metastasis is long-standing. In fact, the clinical observation that thrombocytosis occurs in patients with solid tumors was made more than 100 years ago.[1] One of the first medical reports dealing with the association between thrombosis and cancer dates back as far as 1823, in the works of Jean-Baptiste Bouillaud, a French physician. In 1865, Armand Trousseau, who was also a French physician, published a paper discussing the association between malignant tumors and thrombosis.[2]

Ironically, Trousseau died in 1867 due to malignancy associated with thrombosis, which is why this condition was later termed Trousseau syndrome.

There are three factors (Virchow's triad) that have the most important role in the etiopathogenesis of thrombosis- damage to the endothelium of blood vessels (the most important factor), circulatory stasis or turbulence, and hypercoagulability. Normal blood flow is laminar; platelets are in the center of the blood vessel, separated from the endothelium by a slower plasma zone. Hypercoagulability may be primary (genetic) and secondary (acquired) which occurs in cases of cancer. Pathogenesis of secondary thrombotic diathesis is complex and multifactorial; one of the explanations of hypercoagulability in malignancies refers to the release of procoagulant substances from tumor cells, thereby increasing the possibility of thrombosis.[3]

An elevated platelet count in peripheral blood (thrombocytosis), among other factors, contributes to an increased risk of thrombosis and represents a predictor of poor prognosis of malignant diseases. The mechanisms underlying this surge in platelets as well as its biologic significance are not well understood and are the focus of the current study (Figure 1).

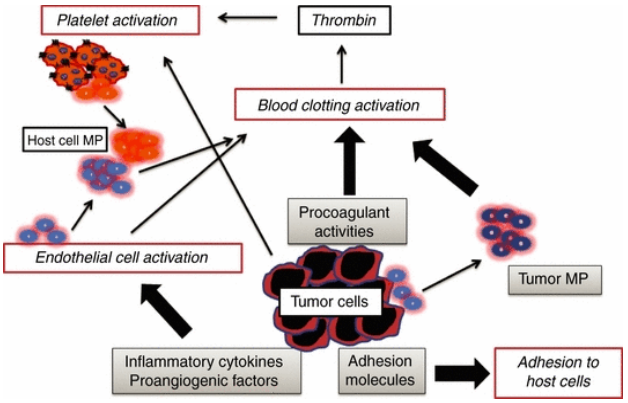

Figure 1: Tumor-hemostatic system interactions.

Beyond clinical observations, experimental evidence suggests that platelets actively promote cancer progression through diverse mechanisms, including protection of cancer cells from immune surveillance, negotiation of cancer-cell arrest in the micro-vasculature, and stimulation of angiogenesis.[4]

Platelet count may be elevated for unknown reasons (essential thrombocytosis), as well as under the influence of various stimuli such as infection, bleeding, presence of tumor process, splenectomy, trauma, anemia (secondary thrombocytosis). Approximately 80% of these cases in fact represent cases of secondary thrombocytosis, which has no specific symptoms and for which no racial, gender or age preference has been proven. Of laboratory analyses, the diagnostic process includes complete blood count with leukocyte formula and sedimentation rate, C-reactive protein, fibrinogen, prothrombin time, and partial thromboplastin time. Further diagnostics may also include ultrasound/CT of the abdomen (hepatomegaly, splenomegaly) and bone marrow biopsy. The treatment includes treatment of the underlying disease, with the addition of low-dose aspirin to prevent the occurrence of thromboembolic complications.[5]

Risk factors and biomarkers associated with the occurrence of thrombosis in cancer patients are numerous and may be classified into patient-related factors, relevant laboratory analyses, factors associated with the malignant disease itself, and factors related to the administered medical treatment.[6,7] Patient-related factors are old age, female gender, race (yellow race is at a lower risk, black race is at a higher risk), comorbidity (associated lung or kidney diseases, infections, hypertension), obesity, smoking, previous deep venous thrombosis, lower performance status. Relevant laboratory analyses are platelets $\geq$350,000/mm^3, leukocytes >11,000/mm^3, hemoglobin <10g/dl, increased value of D-dimer, increased value of C-reactive protein, elevation of tissue factor. Factors associated with the underlying disease- primary site of the tumor (increased risk in cases of pancreatic, stomach, brain, kidney, or lung tumor, tumor of the uterine body, and ovarian tumor), advanced stage of the disease, histological type of tumor. Factors related to the administered medical treatment are- surgery, chemotherapy (cisplatin), hormone therapy, antiangiogenic agents (bevacizumab, sunitinib, sorafenib), immunomodulatory agents (thalidomide, lenalidomide), erythropoesis-stimulating agents, transfusion, central venous catheter.[8]

Khorana risk score categorizes cancer patients into patients with low (0), intermediate (1-2) and high ($\geq$3) risk of venous thromboembolism.[9] Parameters of risk of venous thromboembolism in cancer patients according to the Khorana risk score with points: type of cancer (stomach, pancreas- 2 points), (lung, lymphoma, gynecologic cancers, bladder, testicular- 1 point), BMI ($\geq$35kg/m^2), leukocytes (>11,000/mm^3), platelets (>350,000/mm^3), hemoglobin (<10 g/dl) (Table 1).[10]

Table 1: Risk of venous thromboembolism in cancer patients according to the Khorana risk score (KRS).

Parameters	Points
Type of cancer	
-Stomach, pancreas	2
-Lung, lymphoma, gynecologic cancers, bladder, testicular	1
BMI	$\geq$35 kg/m^2
Leukocytes	>11,000/mm^3
Platelets	>350,000/mm^3
Hemoglobin	<10 g/dl

Tumor cells activate the coagulation process in various ways. Tumor cells may release procoagulant tissue factor,

cancer procoagulant and microparticles (MP) that can directly activate the coagulation cascade. Tumor cells may also activate the host's hemostatic cells (endothelial cells and platelets), by either release of soluble factors or by direct adhesive contact, thus further enhancing clotting activation.[11] Low molecular weight heparin, the drug of choice for DVT, causes the inhibition of Factor X, thereby preventing increased blood clotting and tumor growth. In addition, a tumor cell also produces tissue factor which enhances coagulation. The activity of tissue factor is influenced by an inhibitor from plasma, whose activity is stimulated by low molecular weight heparin. In this way, low molecular weight heparin slows tumor growth and affects the quality of life of patients with malignancy.[12]

Anticoagulants in clinical practice are heparin for intravenous administration, low molecular weight heparin for subcutaneous administration, and oral anti-coagulant preparations. The effect of coumarin-type drugs is reflected in the decreasing levels of prothrombin and factors VII, IX and X in the plasma, which indicates that warfarin, for example, has a strong suppressive effect on the synthesis of these factors in the liver.[13] Warfarin binds to active sites in the enzyme processes of synthesis of prothrombin and other coagulation factors, blocking the binding of vitamin K to these sites, thereby also blocking its action. After the administration of an adequate dose of warfarin, coagulation activity of blood drops to 50% after 12 hours and to 20% after 24 hours. After stopping treatment, coagulation is normalized in 1 to 3 days.[14]

New oral anticoagulants (NOACs) are a new achievement in the management of thrombosis; they directly inhibit factor Xa or thrombin. These agents are very attractive as they can be taken orally, without the need of dose adjustment, they also do not have drug interactions, and moreover, they do not require monitoring. Dabigatran, a direct thrombin inhibitor, and rivaroxaban and apixaban, two direct factor Xa inhibitors, are the most developed agents.[15]

The aim of this study was to prove the frequency of thrombocytosis in patients with cancer, and the importance of anticoagulant therapy. There are many articles with this theme, the problem is topical, but still there is no common opinion about application of anticoagulant therapy in oncology patients.

High risk of bleeding and necessity of monitoring prothrombin time have an effect of this therapy application to be sporadic and to depend on the risk for every individual patient.

METHODS

A retrospective study has analyzed 146 patients who were hospitalized at the Clinic of Oncology of the University Clinical Centre, Banja Luka and the Day Oncology Hospital of the Hospital for Surgical and Internal Medicine "S.tetik", Banja Luka in the period between 2009 and 2014, for chemotherapy. These were patients with malignant breast tumor, gastro-intestinal tumor, or with gynecological malignancies. In the observed sample, we analyzed 38 patients with histologically confirmed malignant tumors of different primary localization, for whom thrombocytosis was detected in the time of diagnosing the disease. All examinees were analyzed by sex, age, primary site of tumor, presence of comorbidity, relevant laboratory analyses, previous blood transfusion, and clinical stage of the disease at the time of disease diagnosis (metastatic or localized disease). Laboratory analyses were done at Central Laboratory University Clinical Centre Banja Luka. Medical documentation was used from the archive Clinic of oncology University Clinical Centre Banja Luka et Day Oncology Hospital of the Hospital for Surgical and Internal Medicine "S.tetik", Banja Luka.

RESULTS

In the analyzed sample consisting of 146 cancer patients, at the time of disease diagnosis thrombosis was detected in 38 patients (26%). Of these 38 patients, 20 were female (52.6%) and 18 were male (47.4%). The patients were aged between 39 and 74 years, with the average age of 63.2 years. Primary breast tumor was diagnosed in 9 female patients, ovarian cancer in 3 of them, and uterine tumor was diagnosed in 2 female patients. Colorectal cancer was diagnosed in 11 patients (8 male patients and 3 female ones), cancer of the stomach in 8 (6 male, 2 female), while pancreatic cancer was diagnosed in 5 patients (4 male, 1 female).

In our patients, the platelet count in peripheral blood ranged from 350,000 to 1,080,000 as the highest value recorded, in a patient with breast cancer. Through the follow-up of the disease course, DVT (deep venous thrombosis) was found in 13 patients (34.2%), which is why further diagnostics was carried out and anticoagulant therapy was administered, with DVT treatment protocol. In 12 patients a deep venous thrombosis of lower extremities was found, while one patient with ovarian cancer was diagnosed with subclavian thrombosis, for which she was treated in the hospital. Patients who were not on anticoagulant therapy because they had no thrombotic manifestations (25 patients, or 65.8%), which means that no further diagnostics in this direction was carried out, were analyzed retrospectively. It turned out that, in the first 6 months after the diagnosis, 2 patients in this group experienced the development of a clinical presentation of massive pulmonary embolism with fatal outcome. These two patients were a female patient aged 67 with disseminated breast cancer and a male patient aged 72 with disseminated cancer of the stomach. In these patients, Khorana scores were 4 and 5, which means that they were in the high-risk category for developing thromboembolic disease. In one patient with rectal cancer (T1N0M0), pulmonary embolism developed a year after the disease had been diagnosed. Thanks to the

emergency hospitalization and therapeutic treatment, this patient is now subject to regular oncological and cardiac examinations, with anticoagulant therapy.

Of the 13 patients who experienced the development of DVT, in 4 patients the leukocyte (L) count was above 11,000/mm^3, while hemoglobin (Hb) level was under 10 g/dl; these included 2 patients with malignant neoplasm of the stomach, one patient with pancreatic cancer, and one female patient with breast cancer, with thrombocytosis. Thus, the Khorana scores were 5 (stomach and pancreas) and 3 (breast).

In 9 of these 13 patients (69%) who experienced the development of DVT, presence of more than 3 comorbidities was found, mainly hypertension, diabetes and cardiomyopathy.

Two patients had previously received blood transfusion; one from the group with DVT and another from the group of those who did not develop signs of thrombosis.

Of the 13 patients with DVT, 7 (54%) were disseminated disease cases. In 2 patients with pulmonary embolism and fatal outcome, the disease was also metastatic (clinical stage 4).

DISCUSSION

Approximately 20% of all cases of venous thromboembolism occur in cancer patients. An assumption is that one in seven patients with malignancy die as the result of pulmonary embolism, not of cancer.

A review of worldwide studies implies that many studies have confirmed the importance of certain risk factors related to the cancer patient in the occurrence of venous thromboembolism (VTE). Primary tumor sites with an increased risk are pancreas, stomach, lungs, body of the uterus, ovaries and kidneys. In addition, studies have shown that there is a higher risk of VTE in cases of lung adenocarcinoma (9.9%) than in cases of squamous cell lung cancer (7.7%), (HR 1.9; CI 1.7-2.1).[16] According to the CCI (Charlson comorbidity index), the presence of comorbidity significantly increases the risk of venous thromboembolism, especially in association with infection, kidney and lung diseases, and obesity.[17] Patients with previous deep venous thrombosis were at a 6 to 7 times higher risk of the repeated disease process in comparison with cancer patients who had not previously experienced this pathological condition.[18] Some studies have shown that a disseminated disease significantly increases the risk of VTE, compared to a disease without metastasis (OR=19.8; 95% CI=2.6-149).[19] Chemotherapy increases the incidence of thromboembolic events, which is explained by the potential iatrogenic damage to the endothelium of blood vessels and an increased synthesis and activation of coagulation factors. Prichard et al have demonstrated that the risk of venous thrombosis in female patients with breast cancer treated with tamoxifen amounts to 1.4%, while it amounts to 9.6% in patients treated with Tamoxifen and chemotherapy.[20] In patients undergoing radiotherapy, the risk of thromboembolic complications is increased because of potential radiation-induced endarteritis and possible increased platelet production. Surgical procedures, immobilization, blood transfusion, and placed central venous catheter also represent important risk factors for the occurrence of thromboembolic complications, as often referenced in the literature. By observing the period of VTE development, Blom et al have demonstrated that there is the highest risk of VTE in the first three months from the diagnosis, with a high risk during the first year, after which the risk decreases. After ten years, the risk is almost negligible.[21]

Results of certain recent worldwide studies on the prophylactic use of anticoagulant therapy in patients with solid tumors who receive outpatient chemotherapy have been published. SAVE-ONCO, one of the largest studies of its kind with 3,000 respondents, served to compare patients taking semuloparin (once a day) and those taking placebo. A significant reduction of VTE was demonstrated in patients taking semuloparin (1.2% vs. 3.4%; HR=0.36; p<0.001).[22] PROTECHT study analyzed patients at "high risk" according to the primary site of tumor, comparing patients taking nadroparin with those taking placebo; again, a reduction in VTE incidence was demonstrated (2.0% vs. 3.9%).[23] However, both these studies have demonstrated an increase in the incidence of bleeding as a complication of anticoagulant therapy; therefore, caution is suggested.

According to the National Comprehensive Cancer Network NCCN, International clinical practice guidelines, American Society of Clinical Oncology ASCO and European Society for Medical Oncology ESMO, it has been confirmed that routine prophylaxis of VTE in cancer patients receiving outpatient chemotherapy is not to be administered.[24-28]

CONCLUSION

In conclusion, from our research, as well as according to the data of scientific literature concluded that thrombocytosis represents a prediction factor for the occurrence of thromboembolic complications in cancer patients.

By reviewing numerous oncology allegations worldwide, one may conclude that there is no consensus on the administration of preventive anticoagulant therapy in cancer patients. Depending on a number of patient-related parameters, factors associated with the underlying disease, therapeutic treatment being administered, diagnostics, and other factors, an individual decision is made for each patient. In the clinical practice, categorization into low, intermediate and high risks of thromboembolic complications in patients with malignancies, according to the Khorana risk score, would be useful; based on parameters obtained in this way,

anticoagulant or antiplatelet therapy is administered. It is necessary to introduce a strict selection of patients who would be submitted to prophylactic anticoagulant therapy, with continuous monitoring. This therapy is most beneficial for patients at "high risk", that is, for patients in the stage 4 of the disease with the primary digestive localization (pancreas, stomach). It can be concluded from our study that patients who were treated with anticoagulant therapy did not experience late thromboembolic events. However, one should always bear in mind the possibility of bleeding as a complication of the anticoagulant therapy, as well as the need for frequent monitoring of prothrombin time values, which further complicates the already complex oncological treatment.

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