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MULTIPLE MYELOMA AND DEEP VEIN THROMBOSIS/PULMONARY THROMBOEMBOLISM – INCIDENCE AND RISK FACTORS

MUPLI MIJELOMOM I DUBOKA VENSKA TROMBOZA/PLUĆNA TROMBOEMBOLIJA – UČESTALOST I FAKTORI RIZIKA

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Summary

Introduction. Deep vein thrombosis and pulmonary thromboembolism are among the most important causes of morbidity and mortality in cancer patients. They are common and serious complications that are affected by various risk factors. The aim of this study was to determine the incidence of thromboembolic complications and their association with risk factors in patients with newly diagnosed multiple myeloma. **Material and Methods.** A retrospective study included 32 patients and the following variables were collected: age, C-reactive protein, beta-2 microglobulin, hemoglobin, platelets, total proteins, nephrotic syndrome, fibrinogen, D-dimer, albumin, lactate dehydrogenase, creatinine, calcium, gender, performance status, type of multiple myeloma, clinical stage, and applied therapy. All variables were compared between two groups of patients: group with thromboembolic complications (deep venous thrombosis and pulmonary thromboembolism), and the group without these complications. **Results.** The study sample included 18 men and 14 women. The patients' age ranged from 36 to 73 years. Of the 32 patients, 6 had deep venous thrombosis of the lower extremities, and 2 patients had deep venous thrombosis and pulmonary thromboembolism. The only two biomarkers that showed an association with venous thromboembolism in our patients with myeloma were elevated levels of C-reactive protein and D-dimer. **Conclusion.** The incidence of thromboembolic complications in patients with newly diagnosed multiple myeloma was 25%. When making the diagnosis of myeloma, risk factors that were significantly associated with venous thromboembolism were elevated levels of C-reactive protein and D-dimer. The occurrence of venous thromboembolism in patients with multiple myeloma was not associated with significantly higher mortality compared to patients without venous thromboembolism.

Key words: Multiple Myeloma; Venous Thrombosis; Pulmonary Embolism; Risk Factors; C-Reactive Protein; Fibrin Fibrinogen Degradation Products; Incidence; Neoplasms

Introduction

Multiple myeloma is a malignant disease from the group of B-cell proliferative diseases characterized by clonal proliferation and accumulation of pathologically altered plasma cells in the bone mar-

Sažetak

Uvod. Duboka venska tromboza i plućna tromboembolija su među najvažnijim uzrocima morbiditeta i mortaliteta kod pacijenata sa karcinomom. Predstavljaju česte i ozbiljne komplikacije na koje utiču različiti faktori rizika. Cilj ovog rada je da se utvrdi učestalost tromboembolijskih komplikacija i njihova povezanost sa faktorima rizika kod pacijenata sa novodijagnostikovanim multiplim mijelomom. **Materijal i metode.** Retrospektivnom studijom obuhvaćena su 32 pacijenta i praćene su sledeće varijable: starost, C-reaktivni protein, beta-2-mikroglobulin, hemoglobin, trombociti, ukupni proteini, nefrotski sindrom, fibrinogen, D-dimer, albumin, laktat dehidrogenaza, kreatinin, kalcijum, pol, performans status, tip multiplog mijeloma, klinički stadijum i primenjena terapija. Sve ove varijable poređene su između dve grupe: grupe pacijenata sa tromboembolijskim komplikacijama (duboka venska tromboza i plućna tromboembolija) i grupe pacijenata bez navedenih komplikacija. **Rezultati.** Unutar posmatranog uzorka bilo je 18 muškaraca i 14 žena. Starost pacijenata je bila od 36 do 73 godine. Od 32 pacijenta, šest je imalo duboku vensku trombozu donjih ekstremiteta, a dva pacijenta udruženu duboku vensku trombozu i plućnu tromboemboliju. Jedina dva biomarkera koja su pokazala povezanost sa venskim tromboembolizmom u našoj grupi pacijenata sa mijelomom bili su povišeni nivoi C-reaktivnog proteina i D-dimera. **Zaključak.** Incidencija tromboembolijskih komplikacija kod pacijenata sa novodijagnostikovanim multiplim mijelomom iznosila je 25%. Faktori rizika pri dijagnozi mijeloma koji su bili značajno udruženi sa pojavom venskog tromboembolizma su povišene vrednosti C-reaktivnog proteina i D-dimera. Pojava venskog tromboembolizma kod pacijenata sa multiplim mijelomom nije bila povezana sa značajno većim mortalitetom u poređenju sa pacijentima bez venskog tromboembolizma.

Ključne reči: multipl mijelom; venska tromboza; plućna embolija; faktori rizika; CRP; D-dimer; incidenca; karcinomi

row [1]. The annual incidence of multiple myeloma is up to 3 per 100,000 individuals, accounting for about 1% of all diagnosed neoplasms and 10% of all hematologic malignancies (second only to non-Hodgkin's lymphoma). In Europe, 40,000 new cases were diagnosed in 2015, and it is estimated that

Abbreviations

VRd	– bortezomib, lenalidomide, and dexamethasone
VTE	– venous thromboembolism
DVT	– deep venous thrombosis
PTE	– pulmonary thromboembolism
VAD	– vincristine, doxorubicin and dexamethasone
CRP	– C-reactive protein
β 2M	– β -2 microglobulin
LDH	– lactate dehydrogenase
CS	– clinical stage
PS	– performance status
BJ	– Bence-Jones type

the number will increase to 46,000 by 2025 [2]. The estimated world-wide 5-year prevalence is approximately 230,000 patients [3]. The five-year survival rate varies from 23 – 47% [4]. The diagnosis of multiple myeloma is based on the presence of more than 10% of pathological monoclonal plasma cells in the bone marrow, serum/urine monoclonal protein, one or more parameters indicating organic dysfunction caused by myeloma activity (calcium elevation, renal dysfunction, anemia and bone disease), and presence of one or more biomarkers of active diseases [5].

Typically, patients are treated with approximately 3 to 4 cycles of induction therapy with bortezomib, lenalidomide, and dexamethasone (VRd) prior to stem cell harvest [6]. In patients under the age of 65 years without pronounced comorbidities after introductory triplet therapy, the treatment is continued with high-dose chemotherapy based on melphalan and autologous hematopoietic stem cell transplantation [7].

Venous thromboembolism (VTE) is the third most prevalent acute cardiovascular syndrome after myocardial infarction and stroke, and it is associated with a significant disease burden [8]. The VTE includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) and it is an important cause of morbidity and mortality among patients with cancer [9]. Results of a recent population-based cohort study showed that the presence of cancer is associated with a 9-fold increased risk of VTE [10]. It is estimated that approximately 4 – 20% of cancer patients will experience VTE at some stage, with the rate being the highest in the initial period following the diagnosis. Annually, 0.5% of cancer patients will experience thrombosis, compared with a 0.1% incidence rate in the general population [11]. In the long term, VTE is a chronic disease and about 30% of all patients with VTE have a recurrence within 10 years [12]. The pathophysiology of venous thrombosis has been famously described by Rudolf Virchow, known as the Virchow's triad, which includes stasis, endothelial injury, and hypercoagulability [13]. The pathogenesis of DVT in cancer patients is multifactorial. All aspects of the Virchow's triad, prolonged immobilization of the patient, application of various therapies (chemotherapy, growth factors, and angiogenesis inhibitors) and surgical interventions that lead to endothelial damage and hypercoagulability associated with cancer, contribute to significantly more frequent DVT in patients with malignant diseases [14].

Several patient-, treatment-, and tumor-related factors affect the risk of VTE in cancer patients [15]. Reasons for higher risk of VTE in the first few months after cancer diagnosis are likely related to intensive therapy (surgical, radiation, and systemic) and a higher tumor burden at the time of diagnosis that decreases with effective therapy. It should also be noted that older studies did not adjust for the competing risk of death when estimating the cumulative incidence of cancer-associated thrombosis and therefore may have overestimated early incidence of some particularly lethal tumors. The overall incidence of VTE in cancer patients has continued to increase over time [16]. This may be due to multiple factors, including increased detection by serial imaging for staging purposes, changes in treatment, which may be more thrombogenic, and longer survival of patients with multiple cancers, therefore increasing an individual's time at risk of VTE [17]. More recently, tumor genetic characteristics also appear to play a role in VTE formation, since genetic profiling demonstrated that mutations in K-ras in colon and lung cancer show an association with increased risk of VTE [18]. The first report of an increased incidence of VTE in patients with newly diagnosed multiple myeloma dates back to 1999. The incidence was 10% and these were patients receiving vincristine, doxorubicin and dexamethasone (VAD) or high doses of cyclophosphamide. Since then, numerous papers have been published on the incidence of thromboembolic complications in patients with multiple myeloma, whether newly diagnosed, refractory or relapsing [19]. Despite thromboprophylaxis, the incidence of VTE with contemporary immunomodulatory drug-based regimens is 6 – 7% [20].

Patients with cancer who survive VTE are at risk of the consequences of the initial event, such as increased bleeding, post-thrombotic syndrome, pulmonary hypertension, and recurrent VTE. The diagnosis of VTE remains a challenge, since it is often asymptomatic. In one prospective study of hospitalized patients, the rate of pulmonary thromboembolism was 1%, but the diagnosis was not made in 70% of patients who died of acute PE, which was detected at autopsy. However, VTE is one of the most common causes that can prevent and reduce the mortality of cancer patients, which makes prophylaxis crucial in this high-risk group of patients. Effective thromboprophylaxis has been shown to reduce morbidity and mortality due to cancer-related thrombosis. According to international guidelines, low molecular weight heparin is the first choice for initial and long-term treatment of VTE and has largely replaced unfractionated heparin and oral vitamin K antagonists, such as warfarin, due to a 50% lower risk of recurrent VTE and similar rates of major bleeding [21–23].

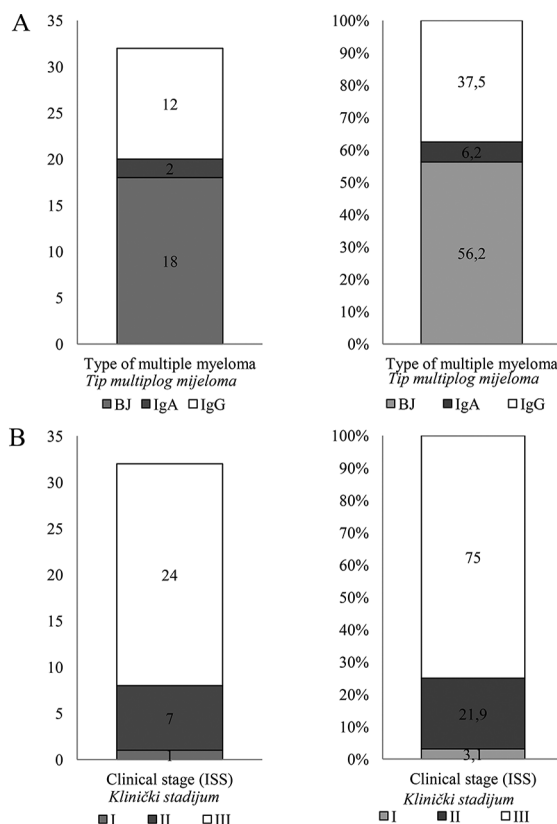
The aims of our study were to determine the incidence of thromboembolic complications (DVT and pulmonary thromboembolism) in patients with newly diagnosed multiple myeloma and to examine the association of risk factors in the diagnosis of the disease with the occurrence of DVT/pulmonary thromboembolism.

Material and Methods

The retrospective study included 32 patients with newly diagnosed multiple myeloma who were diagnosed, treated and systematically followed-up at the Hematology Clinic of the Military Medical Academy, Belgrade, Serbia. The diagnosis and treatment of multiple myeloma was carried out according to the current European Society for Medical Oncology guidelines in the period from 2014 to 2017. This study was approved by the relevant Ethics Committee. The following characteristics were monitored: age, C-reactive protein (CRP), $\beta 2$ microglobulin ($\beta 2M$), hemoglobin, platelets, total protein, nephrotic syndrome, fibrinogen, D-dimer, albumin, lactate dehydrogenase (LDH), creatinine and calcium. Non-parametric variables monitored in the study were: gender, performance status (PS) (0 or 1 vs ≥ 2), type of multiple myeloma (immunoglobulin A, immunoglobulin M, Bence-Jones), clinical stage (CS). According to the international prognostic index patients were stratified into stages I – III, and applied therapy (based on thalidomide, bortezomib and combined VAD chemotherapy). All patients receiving VAD polychemotherapy had a central venous access. All these variables were compared between two groups: group of patients with thromboembolic complications (DVT and PTE), and group of patients without these complications. Statistical data processing was performed using the software package SPSS 20. The calculated parameters for numerical features were described as: mean, standard deviation, and median; in the analysis of the non-parametric features, the characteristics were expressed as a percentage. The frequency of non-parametric phenomena among groups was compared with the Chi-square test (Cross table, Chi-square). Student's t-test for two independent samples compared the values of numerical features by groups. The statistically significant difference was set at $p < 0.05$.

Results

Within the observed sample of 32 patients with multiple myeloma, there were 18 men (56.3%) and



Graph 1. Other characteristics of patients with multiple myeloma show that more than 56% of patients had Bence-Jones type myeloma (A), the most common clinical stage was the third in 75% of patients (B).

Grafikon 1. Ostale karakteristike pacijenata sa multipnim mijelomom pokazuju da je više od 56% pacijenata imalo Bens Dožnsonov mijelom tipa (A), najčešći klinički stadijum je bio treći kod 75% pacijenata (B)

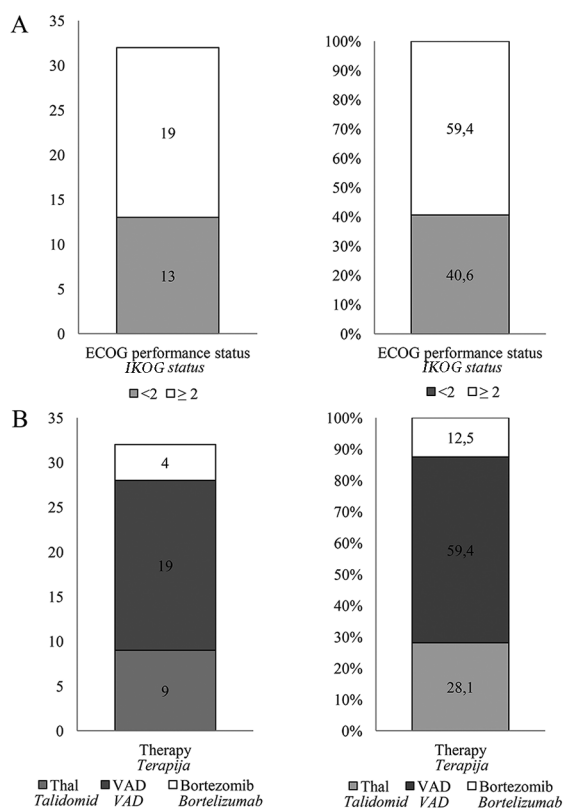
Legenda: BJ – Bens Džonsonov

14 women (43.7%). The laboratory test results at the time of diagnosis of myeloma (**Table 1**) showed elevated CRP in 17 patients (53.1%), 30 patients had

Table 1. Laboratory test results at the time of multiple myeloma diagnosis

Tabela 1. Laboratorijske karakteristike pacijenata u vreme dijagnoze multiplog mijeloma

Variables/Varijable	Value/Vrednost	Number of patients/Broj pacijenata
CRP/C-reaktivni protein	> 5 mg/l	17 (53.1%)
$\beta 2M$ /Beta 2 mikroglobulin	> 2.2 mg/l	30 (93.8%)
Hemoglobin/Hemoglobin	< 100 g/l	21 (65.6%)
Platelets/Trombociti	> $350 \times 10^9/l$	3 (9.4%)
Total proteins/Ukupni proteini	> 84 g/l	13 (40.6%)
Nephrotic syndrome/Nefrotski sindrom	> 3.5 g/l	15 (46.9%)
Fibrinogen/Fibrinogen	> 4.5 g/l	15 (46.9%)
D-dimer/D-dimer	> 0.5 ng/ml	18 (56.2%)
Albumins/Albumini	< 30 g/l	17 (53.1%)
Lactate dehydrogenase/Laktat dehidrogenaza	> 280 IU/l	18 (56.2%)
Creatinine/Kreatinin	> 177 mmol/l	13 (40.6%)
Calcium/Kalcijum	> 2.75 mmol/l	8 (25%)



Graph 2. Eastern Cooperative Oncology Group (ECOG) performance status of patients with multiple (A) and most commonly used therapy (B)

Grafikon 2. Istočna korporativna onkološka grupa (IKOG) performans status pacijenata sa multiplim mijelomom (A) i terapijski pristupi (B)

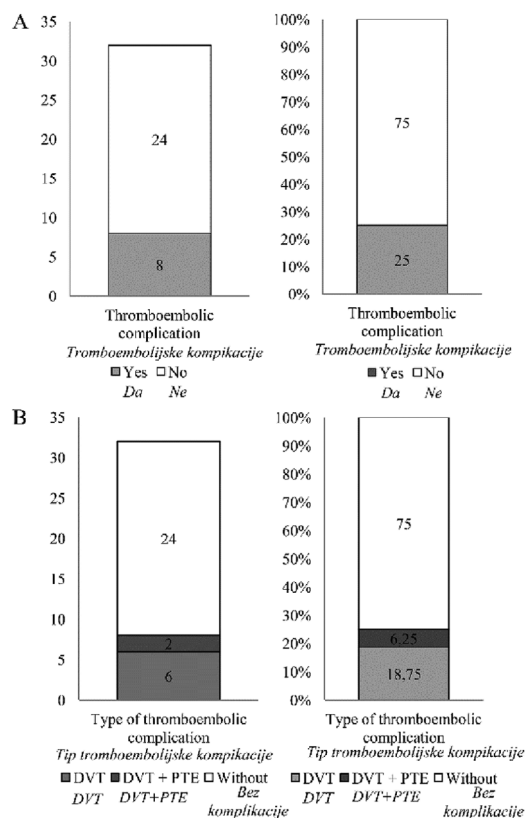
Legenda: IKOG – Istočna korporativna onkološka grupa, VAD – vinskrustin, doksorubicin, deksametazon

elevated $\beta 2M$ and 18 patients (56.2%) had elevated levels of D-dimer (> 0.5 ng/ml). Also, more than half of the patients had anemia (65.6%), hypoalbuminemia (53.1%) and elevated LDH (56.2%).

Slightly more than 56% of patients had Bence-Jones type (BJ) myeloma; the most common CS was III in 75% of patients, and unfavorable PS was found in 59.4% (**Graph 1**). The most commonly used therapy was the VAD protocol in 19 patients, thalidomide-based therapy in 9 patients, while bortezomib-based therapy was the least common in 4 patients (**Graph 2**).

Of the 32 patients, some type of thromboembolic complication was confirmed in 8 (25.0%), DVT of the lower extremities was confirmed in 6 patients, and 2 patients had combined DVT and PTE. None of the patients with central venous access developed DVT at the site of placement. In 3 patients, DVT occurred in the first month after the diagnosis of the disease, while the other 5 developed thrombosis during treatment ranging from 3 to 5 months (**Graph 3**).

When comparing the characteristics of patients with DVT/PTE in relation to the characteristics of patients without thrombosis (**Table 2**), it can be seen that



Graph 3. Incidence of thromboembolic complications in patients with multiple myeloma

Grafikon 3. Incidencija tromboembolijskih komplikacija kod pacijenata sa multiplim mijelomom

Legenda: DTV – duboka venska tromboza, PTE – plućna tromboembolija

elevated CRP values were statistically significantly more often present in patients with thrombosis compared to patients without DVT ($p = 0.041$), i.e. 7 of 8 patients with DVT had elevated CRP levels. Also, it can be noticed that all 8 patients with DVT had an increased level of D-dimer, which showed a statistically significant difference compared to patients without DVT ($p = 0.004$). Comparing the characteristics of patients with DVT/PTE in relation to the characteristics of patients without thrombosis, no statistically significant difference was observed between sexes, levels of $\beta 2M$, hemoglobin, platelets, total protein, albumin, fibrinogen, creatinine, calcium, and 24-h proteinuria.

Furthermore, there was no statistically significant difference in the development of DVT in relation to PS, CS, or in relation to the applied therapy (thalidomide versus bortezomib versus VAD therapy). No difference in mortality was observed between patients whose course of disease was complicated by DVT, compared to patients without DVT.

Discussion

The association of cancer and thromboembolic complications, including DVT and PTE, is a well-

Table 2. Comparative characteristics of patients with multiple myeloma in relation to the presence of deep venous thrombosis/venous thromboembolism**Tabela 2.** Usporedne karakteristike pacijenata sa multiplim mijelomom u odnosu na prisustvo duboke venske tromboze/plućne tromboembolije

Variables Varijable		DVT/PTE		p/p
		Yes/Da	No/Ne	
Gender Pol	Male/Muški Female/Ženski	6 (33.3) 2 (14.3)	12 (66.7) 12 (85.7)	0.412
CRP/C-reaktivni protein	> 5 mg/l ≤ 5 mg/l	7 (41.2) 1 (6.7)	10 (58.8) 14 (93.3)	0.041
β2M/Beta 2 mikroglobulin	> 2.2 mg/l ≤ 2.2 mg/l	8 (26.7) 0 (0.0)	22 (73.3) 2 (100.0)	1.000
Hemoglobin/Hemoglobin	< 100 g/l ≥ 100 g/l	3 (27.3) 5 (23.8)	8 (72.7) 16 (76.2)	1.000
Platelets/Trombociti	> 350 × 10 ⁹ /l ≤ 350 × 10 ⁹ /l	1 (33.3) 7 (24.1)	2 (66.7) 22 (75.9)	1.000
Total proteins/Ukupni proteini	> 84 g/l ≤ 84 g/l	4 (30.8) 4 (21.1)	9 (69.2) 15 (78.9)	0.684
Nephrotic syndrome/Nefrotski sindrom	Yes/Da No/Ne	3 (20.0) 5 (29.4)	12 (80.0) 12 (70.6)	0.691
Fibrinogen/Fibrinogen	> 4.5 g/l ≤ 4.5 g/l	5 (33.3) 3 (17.6)	10 (66.7) 14 (82.4)	0.423
D-dimer/D-dimer	> 0.5 ng/ml ≤ 0.5 ng/ml	8 (44.4) 0 (0.0)	10 (55.6) 14 (100.0)	0.004
Albumins/Albumini	< 30 g/l ≥ 30 g/l	3 (17.6) 5 (33.3)	14 (82.4) 10 (66.7)	0.423
LDH/Laktat dehidrogenaza	> 280 IJ/l ≤ 280 IJ/l	5 (27.8) 3 (21.4)	13 (72.2) 11 (78.6)	1.000
Creatinine/Kreatinin	> 177 mmol/l ≤ 177 mmol/l	4 (30.8) 4 (21.1)	9 (69.2) 15 (78.9)	0.684
Calcium/Kalcijum	> 2.75 mmol/l ≤ 2.75 mmol/l	2 (25.0) 6 (25.0)	6 (75.0) 18 (75.0)	1.000

known complication in the treatment of oncology and hematology patients. Risk factors of DVT in cancer patients are related to: a) characteristics of the tumor itself, b) characteristics of the patient and associated comorbidities, c) used therapy, and d) various biomarkers.

Similar to other malignant diseases, common risk factors (e.g. diseases of cardiovascular origin, long-term immobility, infections) play a significant role in the pathogenesis of thrombosis in myeloma. In addition to paraproteinemia, which contributes to blood hyperviscosity, various mechanisms contribute to hypercoagulability, such as the interaction of neoplastic plasma cells, bone marrow stromal cells, and effects of multiple inflammatory cytokines on the endothelial cells, most commonly interleukin-6 and vascular endothelial growth factor. High levels of paraproteins affect fibrin polymerization and fibrinolysis. Disturbed balance between procoagulant and anticoagulant factors, impaired protein C activity due to acquired resistance to activated protein C are some of the known and shown mechanisms in the pathogenesis of myeloma thrombosis [24]. In our group of subjects with newly diagnosed myeloma, the incidence of VTE was 25%, which is in line with the results of

previously presented studies. The results of several studies on myeloma that analyzed the association of VTE with the clinical characteristics of the disease showed that advanced myeloma and the degree of hyperviscosity were parameters associated with a more frequent occurrence of thromboembolic complications. In our study, there was no statistically significant difference in the incidence of VTE in relation to CS, elevated total proteins and the presence of nephrotic syndrome. Although it was observed that 7 of 8 patients with VTE belonged to CS III, no statistically significant difference in the occurrence of thrombosis was observed in relation to CS I and II ($p = 0.731$).

The results of published studies also show that hematological blood parameters, such as increased leukocyte and platelet counts and decreased hemoglobin levels, may be associated with a significantly higher incidence of DVT [14]. However, in our study, no association was observed between platelet count and decreased hemoglobin levels with a more frequent occurrence of DVT. Also, other examined parameters (albumin, creatinine, fibrinogen, calcium level, β2M and LDH) were not associated with the occurrence of DVT. One of the risk factors for the development of DVT as a complication in patients

with multiple myeloma is unfavorable PS (≥ 2), which may be associated with severe damage/fractures of the flat bones and a pronounced pain syndrome that binds patients to bed. However, although almost 60% of patients in our myeloma group had PS ≥ 2 , no significant difference in DVT was observed compared to patients with PS 0 and 1.

The only two biomarkers that showed an association with DVT in our myeloma patients were elevated levels of CRP and D-dimer. Our results showed that elevated CRP levels were found in 7 out of 8 patients with DVT ($p = 0.041$). The CRP is known to be a marker of systemic inflammation. Although some studies have confirmed its association with DVT in cancer patients, other studies in patients with chronic myeloproliferative neoplasms have not confirmed its importance [14]. In our study, all patients with myeloma and VTE had elevated levels of D-dimer ($p = 0.004$) which is consistent with the results of some studies [25]. As D-dimer is the primary degradation product of fibrin and reflects the global activation of the coagulation and fibrinolytic system, it is expected that its increased level is associated with thromboembolic complications, which was shown in our study.

Immunomodulatory/cereblon-binding agents are the basic therapy for multiple myeloma at all phases of therapy. While these agents are generally well tolerated, increased risk of VTE presents a clinical challenge. This challenge is compounded by the lack of rigor, prospective trials of thromboprophylactic regimens for VTE prevention in these vulnerable patients [26]. The highest risk of VTE in multiple myeloma patients is associated with receiving immunomodulatory agents such as thalidomide or lenalidomide, which is exacerbated by the concomitant use of high dose steroids [27]. The incidence of thrombosis in multiple myeloma is less than 5% for thalidomide alone, versus 10 - 20% for thalidomide with dexamethasone and 20 - 40% for thalidomide with chemotherapy [28]. In a randomized trial on lenalidomide with either high-dose or low-dose dexamethasone, the incidence of VTE was 26% and 12%, respectively [29].

The patients included in this study mostly received VAD polychemotherapy (19 patients), followed by combination therapy based on thalidomide (combinations with dexamethasone and cyclophosphamide or with dexamethasone and doxorubicin) (9 patients). Bortezomib-based therapy was the least commonly used (4 patients). There was no statistically significant difference in the incidence of DVT in regard to the applied therapy ($p = 0.841$), i.e. 4 out

of 15 patients on VAD therapy, 3 out of 6 patients on thalidomide and 1 out of 4 patients on bortezomib developed DVT. Considering the applied combination therapy, the incidence of DVT in our patients was similar to that in other study groups. Bortezomib, a proteasome inhibitor, is the drug that has so far shown the lowest incidence of thromboembolic complications (0 - 1%), either as monotherapy or in combination with dexamethasone. Data from studies that link VTE and inferior overall survival in multiple myeloma patients are conflicting, and a clear association has not been established [30, 31]. Although it has been shown that DVTs are associated with malignant diseases, being the leading cause of death after cancer, our study showed no significant difference in the survival of patients with myeloma in relation to the presence or absence of DVT.

Given that the combined triplet therapy with thalidomide and lenalidomide is accompanied by a significant rate of thromboembolic complications, the American Society of Clinical Oncologists and the European Society of Oncologists recommend preventive use of aspirin or low molecular weight heparin in low-risk and high-risk patients [32, 33]. However, direct-acting oral anticoagulants are becoming increasingly popular. Their profile is favorable, as secondary to safety and efficacy, they are administered orally and do not require routine monitoring. They are currently licensed for use in the treatment of cancer-associated thrombosis [34-36].

Conclusion

The incidence of thromboembolic complications (deep vein thrombosis/pulmonary thromboembolism) in patients with newly diagnosed multiple myeloma was 25%. When making the diagnosis of myeloma, risk factors that were significantly associated with the occurrence of deep vein thrombosis were elevated C-reactive protein and D-dimer.

There was no statistically significant difference in the occurrence of deep vein thrombosis in relation to the type of myeloma, clinical stage of the disease, values of hematological blood parameters, β -2 microglobulin, lactate dehydrogenase, fibrinogen, creatinine levels, total protein, albumin, performance status, or the applied therapy. The occurrence of deep vein thrombosis in patients with multiple myeloma was not associated with significantly higher mortality compared to patients without deep vein thrombosis.

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