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Thromboembolic Risk and Survival Outcomes in Multiple Myeloma Patients Following Autologous Stem Cell Transplantation

Gülşah Akyol[1], Hatice Aslan Sırakaya[2], Şerife Emre Ünsal[1]

[1]*Erciyes University Faculty of Medicine, Department of Hematology, Kayseri, Türkiye*
[2]*University of Health Science Türkiye, Kayseri City Hospital, Clinic of Internal Medicine, Kayseri, Türkiye*

ABSTRACT

Aim: To assess risk factors for venous thromboembolism (VTE) in patients with multiple myeloma (MM) who underwent autologous hematopoietic cell transplantation (HCT).

Methods: This single-center retrospective study included 380 MM patients who underwent autologous HCT. Patients developed VTE were identified by reviewing patients' medical data. In all patients, chemotherapy regimen, remission status, comorbid conditions, age at time of HCT, number of autologous HCTs, disease stage, follow-up duration, immunoglobulin type, and mortality were assessed, and their effects on VTE development were evaluated.

Results: Of the patients included, 63.2% (n=240) were male while 36.8% (n=140) were female. VTE occurred in 40 patients (10.5%). Mean follow-up was found as 41.63±33.84 mounths. Overall, 55.8% (n=212) of the patients died after autologous HCT. A significant correlation was found between older age at the time of HCT and VTE development (p=0.046). The rate of VTE-free patients was higher in patients in remission than in those not in remission (p=0.045).

Conclusion: Remission status and older age at the time of HCT increased the risk of VTE in MM patients who underwent autologous HCT.

Keywords: Venous thromboembolism, multiple myeloma, autologous stem cell transplantation

Introduction

Multiple myeloma (MM) is a malignancy characterized by the neoplastic proliferation of monoclonal plasma cells within the bone marrow. This proliferation often results in osteolytic lesions, osteopenia, or pathological fractures, alone or in combination. It is the second most common hematological malignancy following non-Hodgkin lymphoma.

In recent decades, advancements in MM treatment, including the introduction of novel therapies such as autologous hematopoietic cell transplantation (HCT), immunomodulatory drugs (IMIDs), and proteasome inhibitors, have significantly improved survival rates. Despite these improvements, MM patients who develop venous thromboembolism (VTE) face a threefold increase in mortality risk within the first year after diagnosis [1,2].

The onset of VTE in MM patients is influenced by both intrinsic and extrinsic factors. Tumor cells release prothrombotic factors, while external contributors such as medications, immobility, and the use of indwelling catheters further exacerbate the risk [3]. Among all hematological malignancies, MM patients exhibit the highest rates of VTE, with 4-10% developing VTE at some stage of their disease [4].

The risk of VTE is particularly elevated among MM patients receiving proteasome inhibitors and monoclonal antibodies combined with IMIDs (thalidomide, lenalidomide, and pomalidomide). The thrombogenic potential of IMIDs is attributed to their multifactorial mechanisms of action, and the risk further increases when these agents are used alongside multi-drug chemotherapy and/or high-dose dexamethasone [5,6]. *In vitro* studies have demonstrated that these agents

Address for Correspondence: Gülşah Akyol MD, Erciyes University Faculty of Medicine, Department of Hematology, Kayseri, Türkiye
E-mail: drgakyol@gmail.com **ORCID ID:** orcid.org/0000-0003-1909-5938

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elevate plasma levels of factor VIII and von Willebrand factors, induce protein C resistance, and decrease thrombomodulin levels, all of which contribute to an increased risk of thrombotic events [7,8]. Consequently, several guidelines recommend thromboprophylaxis for MM patients undergoing such therapies.

Numerous studies have investigated the VTE risk associated with drugs used in MM treatment, leading to the development of guidelines to mitigate this risk in patients receiving chemotherapy regimens or allogeneic bone marrow transplantation. However, data regarding VTE rates specifically in MM patients undergoing autologous HCT remain limited.

In this study, we aimed to evaluate the incidence of embolic events in MM patients who underwent autologous HCT, thereby contributing to the understanding of thrombotic complications in this population and to informing thromboprophylaxis strategies.

Methods

Patient Selection

We retrospectively reviewed 380 patients with MM (aged 18-65 years) who underwent autologous HCT and were followed at the Hematology and Bone Marrow Transplant Clinic, Erciyes University Faculty of Medicine, between December 2008 and December 2022.

The study was approved by the Erciyes University Clinical Research Ethics Committee (approval no: 2021/622, date: 22.09.2021). Because the study was designed retrospectively no written informed consent form was obtained from the patients. The study was conducted in accordance with the tenets of the Declaration of Helsinki and applicable patients' rights legislation.

Data were extracted from patients' files and the hospital electronic database. In all patients undergoing autologous HCT, a central venous catheter was inserted into the upper extremity before transplantation. The catheter was left in place until hematopoietic recovery unless an infection was suspected or confirmed. The central venous catheter was flushed weekly, and dressing changes were performed weekly or as needed.

Catheter-related thrombotic events were included in the study. Patients considered eligible for autologous HCT received primary thromboprophylaxis during hospitalization according to institutional standard practice. In addition, patients receiving immunomodulatory agents were administered appropriate anticoagulant or antiplatelet prophylaxis based on their individual thromboembolic risk.

The study included patients aged ≥18 years with available clinical data, who were diagnosed with MM according to the 18th International Myeloma Workshop criteria and underwent autologous HCT [9]. Patients with a history of long-term anticoagulation use due to thrombosis or cardiac arrhythmia, those receiving antiplatelet therapy, those with coagulopathy, and those with a history of VTE were excluded. Data on comorbid conditions, including obesity, cardiac disorders, diabetes mellitus (DM), hypertension (HT), renal failure, and chronic obstructive pulmonary disease (COPD), were extracted from patient files. In addition, information on immunoglobulin type, response evaluation, number of transplants performed, chemotherapy regimen administered, disease stage, remission status, duration of follow-up, age at time of HCT, and mortality was assessed.

The disease response status before autologous HCT was assessed. Patients who achieved at least a partial response (≥PR) before transplantation were classified as good responders, whereas those with a response less than a PR were classified as poor responders.

Identification of Cases with VTE

In this study, the primary endpoint was acute symptomatic VTE, including pulmonary embolism and deep venous thrombosis of the upper or lower extremities. Data were analyzed up to treatment completion or death for all patients.

Imaging studies and reports obtained following the first autologous HCT were screened for thrombosis or embolism. Additionally, we reviewed contrast-enhanced thoracic computed tomography images, ventilation-perfusion scintigraphy, and Doppler sonography of the upper and lower extremities. In all VTE cases, disease status was confirmed using medical records. The secondary endpoint was mortality.

Statistical Analysis

All data analyses were performed using IBM SPSS (SPSS Inc., Chicago, IL, USA), version 22. The normality of the variables was assessed using Kolmogorov-Smirnov tests and graphical analysis. When the study data were analyzed, normally distributed variables were expressed as mean and standard deviation; non-normally distributed variables were expressed as median and interquartile range, and categorical variables were expressed as percentages and counts. Independent t-tests were used to compare quantitative data that were normally distributed, while the Mann-Whitney U test was employed for data with skewed distributions. Qualitative data were compared using Pearson's chi-square test and the Fisher-Freeman-Halton exact test. The presence of DVT and PTE was analyzed using Kaplan-Meier survival analysis, according to Vadborlen 2. A p value <0.05 was considered statistically significant.

Results

A total of 380 patients were included in the study, 63.2% (n=140) of whom were female. No significant difference in gender distribution was observed between the groups (p=0.068). The mean age of the patients was 63.48±9.02 years, while their mean age at the time of HCT was 56.66±8.84 years. VTE occurred in 40 patients (10.5%). The mean age at the time of HCT for the group that developed VTE was 59.30±7.64 years, compared to 56.35±8.93 years for the group that did not develop VTE. This difference was statistically significant (p=0.046).

Among the 40 patients who developed VTE, 9 experienced pulmonary embolism and 3 had catheter-related thrombosis.

One patient developed recurrent VTE; however, this patient was counted as a single case in the analysis. VTE events occurred from the pre-transplant conditioning period through the second month after transplantation, and the majority developed within the first 100 days following transplantation. Only one patient developed VTE during the first year after transplantation, and one additional patient did so during the second year.

While 63.2% of the patients had no comorbidities, 5.8% had DM, 4.7% had HT, 2.9% had heart failure, 2.4% had COPD, 11.3% had renal failure, and 9.7% had two or more comorbidities. The average follow-up duration of the patients was 41.63±33.84 mounths. Among patients in the VTE group, 80% were in remission, compared with 65% in the non-VTE group. This difference was statistically significant (p=0.045) (Table 1).

Table 1. Demographic and clinical characteristics of the patients

	All patients	Non-VTE (n:340)	VTE (n:40)	p value
Sex (male/female)	240/140 (63.2/36.8)	220/120	20/20	[a]0.068
Age	63.48±9.02	63.24±9.06	65.53±8.49	[b]0.130
Age at time of HCT	56.66±8.84	56.35±8.93	59.30±7.64	[b]0.046*
Follow-up (n=374)	41.63±33.84	41.89±33.97	39.45±33.13	[b]0.557
Comorbidity				
None	240 (63.2)	211 (62.1)	29 (72.5)	[c]0.666
DM	22 (5.8)	21 (6.2)	1 (2.5)	
HT	18 (4.7)	15 (4.4)	3 (7.5)	
Heart failure	11 (2.9)	10 (2.9)	1 (2.5)	
COPD	9 (2.4)	8 (2.4)	1 (2.5)	
Renal	43 (11.3)	41 (12.1)	2 (5.0)	
≥2	37 (9.7)	34 (10.0)	3 (7.5)	
Melphalan dose				
200 mg	322 (84.7)	290 (90.1)	32 (9.9)	[a]0.378
140 mg	58 (15.3)	50 (86.2)	8 (13.8)	
Ig type				
IgG/Kappa	132 (35.5)	114 (86.4)	18 (13.6)	[c]0.063
IgG/Lambda	73 (19.6)	70 (95.9)	3 (4.1)	
IgA/Kappa	51 (13.7)	43 (84.3)	8 (15.7)	
IgA/Lambda	34 (9.1)	30 (88.2)	4 (11.8)	
Kappa	50 (13.4)	48 (96)	2 (4)	
Lambda	31 (8.3)	28 (90.3)	3 (9.7)	
Number of autologous HCT				
Two autologous HCT	93 (24.5)	86 (92.5)	7 (7.5)	[a]0.278
One autologous HCT	287 (75.5)	254 (88.5)	33 (11.5)	
Treatment regimens				
VAD	75 (18.4)	70 (94.3)	5 (5.7)	[c]0.113
Bortezomib	260 (67.1)	233 (89.8)	27 (10.2)	
Lenalidomide	45 (10.5)	37 (82.5)	8 (17.5)	
Renal failure				
No	325 (85.5)	289 (88.9)	36 (11.1)	[a]0.395
Yes	55 (14.5)	51 (92.7)	4 (7.3)	
Remission status				
Poor responder (<PR)	82 (16.3)	68 (20%)	14 (35%)	**[c]0.045***
Good responder (≥PR)	298 (73.2)	272 (80%)	26 (65%)	
Mortality				
Non-survivor	212 (55.8)	188 (88.7)	24 (11.3)	[a]0.571
Survivor	168 (44.2)	152 (90.5)	16 (9.5)	

[a]: Pearson chi-square test, [b]: Student's test, [c]: Fisher freeman halton test, *: p<0.05
VTE: Venous thromboembolism, DM: Diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, HCT: Hematopoietic cell transplantation, VAD: Vincristine, adriamycin, dexamethasone, PR: Partial response, IgG: Immunoglobulin G

It was observed that 44.7% of the patients who developed VTE survived, with an average survival time of 64.23±2.69 months, while 40% of the patients who did not develop VTE survived, with an average survival time of 58.20±6.93 months. The last death in the VTE group occurred in the 146th month, whereas in the non-VTE group the last death occurred in the 114th month. At this point, the cumulative survival rate was 0%, with a standard error of 0%. When survival rates were evaluated using the log-rank test, no statistically significant difference in survival was observed between the groups (p=0.305) (Table 2).

Regarding treatment regimens, 53.3% of patients who received vincristine, adriamycin, dexamethasone (VAD) survived, with an average survival time of 91.37±5.52 months. Among those who received bortezomib, 41.5% survived, with an average survival time of 57.09±2.87 months. In the group receiving lenalidomide, 51.1% survived, with an average survival time of 38.47±6.45 months. The last death occurred in the VAD group in the 146th month, in the bortezomib group in the 129th month, and in the lenalidomide group in the 89th month. At these time points, the cumulative survival rate was 0%, with a standard error of 0%. When survival rates were evaluated using the log-rank test, no statistically significant difference was found between the treatment groups (p=0.56) (Table 3).

Discussion

In this study, a significant relationship was found between the development of VTE and the age at which patients underwent autologous HCT. The mean age of patients who developed VTE was significantly lower than that of patients who did not develop VTE. A nother important finding in our study was that patients who developed VTE had a significantly higher remission rate. This may be related to increased life expectancy and greater care requirements.

VTE is a common complication in patients with hematologic and non-hematologic malignancies and is an important cause of morbidity and mortality. With advances in MM treatment and prolongation of the chronic process, VTE has emerged as a common cause of death in this population [10]. In this study, the age at HCT administration was significantly lower in the VTE group than in the VTE-free group. This finding may have developed due to younger patients being exposed to an increased thrombotic risk associated with intensive chemotherapy and immunosuppressive treatments [11-13]. Increased endothelial reactivity, changes in coagulation profiles, or more aggressive treatment approaches applied at a younger age may be considered mechanisms contributing to this. Furthermore, exposure of younger patients to higher cumulative doses of chemotherapy and immunosuppressive agents, due to their longer life expectancy, may contribute to endothelial dysfunction and prothrombotic conditions. More frequent catheterization and invasive procedures in younger patients may also increase the risk of vascular injury and thrombosis [14]. Therefore, early implementation of thromboprophylaxis measures may be recommended in this population.

Another important finding is the higher remission rate among patients who develop VTE. This suggests that patients who achieve remission may face an increased thrombotic risk due to their longer survival and need for continuous treatment [15,16]. To prevent vascular events that may develop in this group, more stringent monitoring and prophylactic strategies may be useful. In addition, it should be considered that remission is associated with ongoing maintenance treatments and that these treatments may affect coagulation pathways [17,18]. In particular, the effects of immunomodulatory agents and corticosteroids on thrombotic risk should be investigated in more detail in future studies.

Although there were no significant differences in survival rates or mean survival times between the VTE and non-VTE groups, the survival rates of patients who developed VTE were observed to be slightly higher than those of patients who did not. This trend can be explained by effective anticoagulant treatment and close clinical monitoring, which reduce long-term mortality from thrombotic events. The survival advantage observed in the VTE group may also be related to the increased frequency of supportive care and monitoring. Among patients diagnosed with VTE, improved survival may be attributable to more comprehensive medical follow-up, including anticoagulant therapy, cardiovascular monitoring,

Table 2. Survival analysis according to VTE

	Non-survivor	Survivor	Survival rate	Mean survival time
Non-VTE (n: 340)	188	152	44.7%	64.23±2.69
VTE (n: 40)	24	16	40.0%	58.20±6.93

Kaplan-Meier analysis
VTE: Venous thromboembolism

Table 3. Survival analysis according to chemotherapy regimens employed

Last treatment before auto-HCT	Non-survivor	Survivor	Survival rate	Mean survival time
VAD (n: 75)	35	40	53.3%	91.37±5.52
Bortezomib (n: 260)	152	108	41.5%	57.09±2.87
Lenalidomide (n: 45)	22	23	51.1%	38.47±6.45

Kaplan-Meier analysis
VAD: Vincristine, adriamycin, dexamethasone, HCT: Hematopoietic cell transplantation

and lifestyle modifications. Based on this, the effects of intensive monitoring protocols on survival warrant further investigation.

In this study, no significant difference was found in survival outcomes between chemotherapy regimens. No statistically significant association was found between the last chemotherapy regimen administered before transplantation and the development of VTE. However, patients receiving VAD had the longest mean survival time, while those receiving lenalidomide had the shortest. This situation highlights the importance of careful risk assessment and supportive measures in high-risk groups. In particular, lenalidomide is known to increase thrombotic risk when used in combination with corticosteroids and this may explain the shorter survival times observed [19-21]. In our cohort, lenalidomide was used as second-line treatment prior to autologous HCT for patients whose disease was refractory to first-line VAD- or bortezomib-based regimens. Accordingly, the shorter mean survival observed among patients treated with lenalidomide most likely reflects the adverse prognosis associated with treatment-refractory disease rather than an independent detrimental effect of lenalidomide. C hemotherapy can induce local inflammation by causing irritation of the vascular endothelium and an imbalance between procoagulant and anticoagulant mechanisms. Studies on the effect of antithrombotic prophylaxis in patients receiving high-risk treatment regimens will provide more guidance in this regard.

The findings of this study highlight the importance of individualized risk assessment in patients undergoing HCT, especially for those who are younger or in remission. Implementation of routine thromboprophylaxis and strict monitoring protocols may reduce morbidity and improve survival outcomes in high-risk groups. Furthermore, larger prospective studies are needed to confirm these associations and elucidate the underlying pathophysiologic mechanisms.

Study Limitations

Some limitations of this study include the relatively small sample size of the group that did not develop VTE, which may limit statistical power and generalizability. Furthermore, the retrospective design poses challenges in establishing causal relationships, and factors such as genetic predispositions, medication compliance, and lifestyle influences could not be fully accounted for. Incorporating such variables into prospective analyses may enhance risk estimation models and improve prevention strategies.

The retrospective and single-center design of our study inherently limits the generalizability of our findings and introduces potential selection bias. We were unable to fully evaluate the impact of unmeasured confounding factors such as patients' genetic thrombophilia profiles, lifestyle habits, and adherence to prophylactic medications outside the hospital setting. Although the overall patient cohort was adequately sized, the relatively small number of patients who developed VTE (n=40) may have limited the statistical power to detect more subtle differences in survival or risk among specific subgroups. Well-designed, multicenter, prospective studies are required to validate our findings and comprehensively identify the independent risk factors for thromboembolic events in this patient population.

Conclusion

Our study highlights the complex relationship among age, remission status, and development of VTE in patients undergoing autologous HCT. Specifically, older age at transplantation and achievement of remission were associated with a higher risk of VTE, emphasizing the need for careful monitoring and individualized treatment strategies. These observational findings advance understanding of thrombotic complications in hematologic malignancies and underscore the importance of proactive management approaches to improve patient outcomes. Future research focusing on prospective studies and incorporating genetic and inflammatory biomarkers may further refine risk stratification and guide targeted interventions.

Ethics

Ethics Committee Approval: The study was approved by the Erciyes University Clinical Research Ethics Committee (approval no: 2021/622, date: 22.09.2021).

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.A., Concept: Ş.E.Ü., Design: Ş.E.Ü., H.S., Data Collection or Processing: H.S., Analysis or Interpretation: G.A., H.S., Literature Search: Ş.E.Ü., Writing: Ş.E.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

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