Effect of prophylactic anticoagulation on incidence of venous thromboembolism in testicular germ cell tumor patients

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Abstract

Background Testicular germ cell tumors (GCTs) are among the most common solid tumors in young males. With the availability of highly effective treatment, improving patients' quality of life has gained more focus in recent years. Venous thromboembolism (VTE), commonly occurring in GCT patients, is associated with increased morbidity and mortality. Prophylactic anticoagulation has been shown to decrease the risk of VTE in patients with malignancy. The aim of this retrospective study was to evaluate the effect of low molecular weight heparin (LMWH) prophylaxis on incidence of VTE and outcome in GCT patients treated with first-line chemotherapy.

Methods Our study population included chemotherapy-naïve GCT patients treated with first-line chemotherapy at the National Cancer Institute, Bratislava, Slovakia from January 2000 to December 2017. VTE was defined as any venous thrombosis or pulmonary embolism, confirmed by imaging, occurring during first-line chemotherapy. Patients diagnosed with VTE on initial staging exam were excluded from the study. No visceral thromboses were observed.

Results Our cohort included 353 GCT patients. LMWH prophylaxis was administered to 104 patients (29.5%), 249 patients (70.5%) did not receive prophylaxis. We observed 14 (4.0%) VTE events. The difference in VTE incidence between patients with and without prophylaxis was not statistically significant (5.8% vs. 3.2% $P = 0.37$). We have observed a trend to longer overall survival in patients without prophylaxis (hazard ratio = 0.61, 95% confidence interval = 0.32-1.13, $P = 0.08$). Patients with extragonadal GCT receiving VTE prophylaxis had significantly shorter survival. (hazard ratio = 0.29, 95% confidence interval = 0.08-1.12, $P = 0.04$). This effect was most likely driven by higher incidence of treatment related deaths in patients with extragonadal GCT receiving LMWH. ($P = 0.06$)

Conclusions LMWH prophylaxis was not associated with decreased VTE incidence. Moreover, there was a higher incidence of treatment related deaths in patients with extragonadal tumor location. LMWH prophylaxis during hospitalization should not be used routinely in GCT patients receiving chemotherapy.

Background

Testicular germ cell tumors (GCTs) represent one of the most common solid neoplasms in young males between the ages of 15 and 35 and the incidence has been steadily rising in the past decades.[1, 2] Cisplatin-based chemotherapy with or without resection of the residual mass are highly effective in the treatment of GCTs with five-year survival rate of more than 95%.[3] As a result, the number of GCT survivors with long life expectancy is rising. Therefore, maintaining patients' quality of life and minimizing treatment-related morbidity and mortality has gained more significant interest in recent years.

Venous thromboembolism (VTE) commonly occurs in cancer patients.[4] It affects about 10% of patients with malignancy. The pathophysiology is thought to be multifactorial and is related to the type of tumor, anatomic location, patient's comorbidities, type of treatment, etc.[5] When compared to patients with different type of malignancy, GCT patients have higher incidence of VTE events.[6]

VTE is associated with increased morbidity and mortality in cancer patients. Levitan et al found more than a threefold higher risk of recurrent VTE and death in cancer patients compared to patients with VTE without cancer diagnosis.[7]

Incidence of VTE in GCT patients has been assessed in a few studies and the results vary widely. Honecker et al observed 9% VTE incidence in patients before starting chemotherapy, while there was only a 2% incidence of VTE during first-line chemotherapy.[8] In a different study, Piketty et al found a 14% incidence of VTE during first-line chemotherapy and 5% incidence of VTE after chemotherapy.[6]

Several groups focused on identification of risk factors of VTE events in GCT patients.[6, 9-12] Weijl et al observed an increased risk of VTE in patients with liver metastases (odds ratio = 4.9).[10] Piketty et al identified body surface area $> 1.9\text{m}^2$ (relative risk (RR) = 5, 95% confidence interval (CI) 1.8-13.9) and elevated serum lactate dehydrogenase (RR = 6.4, 95% CI 2.3-18.2) as independent risk factors. In their study, patients without any risk factors had 4% probability of having VTE, while patients with at least 1 risk factor had 26% probability of having VTE.[6]

Prophylactic anticoagulation has been shown to decrease the risk of symptomatic VTE in cancer patients. (RR = 0.56, 95% CI 0.47-0.68) [13] Gizzi et al studied the incidence of thromboembolic events in GCT patients treated with first-line chemotherapy and observed lower incidence of thromboembolic events in patients receiving thromboprophylaxis when compared to patients without prophylaxis.[12] However, small number of patients in each subgroup of this study makes the interpretation of the results difficult and larger study is needed to elucidate the relationship between thromboprophylaxis and incidence of VTE in GCT patients undergoing cisplatin-based chemotherapy.

The aim of this retrospective study was to evaluate the effect of low molecular weight heparin (LMWH) prophylaxis on incidence of VTE events and outcome in germ cell tumor patients treated with first-line chemotherapy.

Patients And Methods

Study patients

This retrospective study was conducted using the National Cancer Institute medical records database. The study was approved by the Institutional Review Board and waiver of consent form was granted. Patients diagnosed with germ cell tumors treated with first line/adjuvant chemotherapy at the National Cancer Institute, Bratislava, Slovakia from January 2000 to December 2017 were eligible. Patients with any concurrent malignancy, other than non-melanoma skin cancer in the previous 5 years were excluded from the study. Excluded were also patients with previous chemotherapy, patients with venous thromboembolism diagnosed on the initial staging exam and patients on anticoagulation therapy (therapeutic or prophylactic) started before the initiation of first line chemotherapy.

Definition of VTE event

VTE event was defined as any venous thrombosis or pulmonary embolism occurring between Day 1 of first cycle of the first-line chemotherapy and Day 21 of the last cycle of the first-line chemotherapy. Cases of superficial phlebitis were not classified as events. Every VTE event had to be confirmed by imaging studies, either Doppler ultrasonography or a CT scan. Depending on patients' presenting symptoms, the events were divided into symptomatic and incidental, if discovered on imaging done for a different purpose.

Baseline data

During the initial staging, patients had a CT scan of the chest, abdomen and pelvis. Baseline data regarding age, primary tumor location, tumor histology, TNM stage, International Germ Cell Cancer Collaborative Group (IGCCCG) risk class and first-line chemotherapy regimen were recorded. Blood coagulation tests were not routinely performed during the initial screening.

VTE prophylaxis

LMWH prophylaxis was not routinely prescribed before January 2010 during hospitalization. At our institution, all GCT patients are hospitalized during chemotherapy. In December 2007, American Society of Clinical Oncology released clinical practice guidelines recommending prophylactic anticoagulation for hospitalized patients receiving chemotherapy.[14] Therefore, starting in January 2010, we progressively implemented prophylactic anticoagulation with low molecular heparin (nadroparin 0,4 ml or equivalent). However, not all physicians integrated this guideline into their practice and LMWH prophylaxis was prescribed at the individual physician's discretion.

STATISTICAL ANALYSIS

We performed a retrospective review of patients' medical records. All thromboses or pulmonary embolism, confirmed by imaging modality, were classified as events. Patients' characteristics were tabulated and summarized as the median (range) values for continuous variables and frequency (percentage) for categorical variables, respectively. Fisher's exact test was used for statistical analysis to compare VTE events between groups with and without prophylaxis.

Primary outcome was the overall incidence of VTE events occurring between Day 1 of first cycle of the first-line chemotherapy and Day 21 of the last cycle of the first-line chemotherapy. Secondary outcomes were incidences of VTE events in various subgroups and overall survival.

Time to VTE was calculated from the start date of chemotherapy to date of VTE diagnosis. Log-rank test was used to compare the differences between time to VTE between patients with and without prophylaxis.

Median follow-up was calculated as median time of observation of study patients. Overall survival was calculated from the start date of chemotherapy to date of the last follow-up or death of the patient. Kaplan-Meier method was used to estimate overall survival. The log-rank test was used to compare

differences in survival between patients with and without prophylaxis. All calculations were done in NCSS 2019 statistical software.[15]

Results

Patients' characteristics

Our cohort included 353 chemotherapy naive patients with GCTs treated with first line chemotherapy (Flow diagram). Patients' characteristics are summarized in Table 1. Median age of patients at time of enrollment was 32 years (ranging from 17 to 63 years). The majority of patients (75.9%) had non-seminomatous germ cell tumor. All patients received platinum-based chemotherapy.

Table 1
Patients' characteristics

	N	%
All	353	100
Histology		
seminoma	79	22.4
NSGCT	268	75.9
unknown	6	1.7
Primary tumor		
Gonadal	318	90.1
Extragenadal	35	9.9
Retroperitoneum	22	6.2
Mediastinum	10	2.8
Brain	2	0.6
Unknown	1	0.3
Stage		
I.A/B	38	10.8
I.S	22	6.2
II.A	30	8.5
II.B	47	13.3
II.C	44	12.5
III.A	43	12.2
III.B	42	11.9
III.C	87	24.6
IGCCCG Risk Group		
Stage IA/B	38	10.8
Good	192	54.4
Intermediate	46	13.0

NSGCT - nonseminomatous germ cell tumor, IGCCCG - International Germ Cell Cancer Collaborative Group, BEP – bleomycin, etoposide, cisplatin

	N	%
Poor	77	21.8
Treatment regimen		
BEP	250	70.8
Other	103	29.2
Follow-up status		
Alive	300	84.99
Exitus	51	14.45
Unknown	2	0.57
NSGCT - nonseminomatous germ cell tumor, IGCCCG - International Germ Cell Cancer Collaborative Group, BEP – bleomycin, etoposide, cisplatin		

VTE prophylaxis

LMWH prophylaxis was administered to 104 patients (29.5%) for the duration of hospitalization for chemotherapy, 249 patients (70.5%) did not receive LMWH prophylaxis. Before January 2010, 7 out of 174 (4.0%) patients received LMWH prophylaxis and 97 out of 179 (54.2%) patients treated after January 2010 received prophylaxis (Flow diagram). The majority of patients (74.3%) receiving LMWH prophylaxis after January 2010 were stage II.B or higher.

VTE events

In our study population, most VTE events occurred even before starting chemotherapy. We identified 41 out of 394 (10.4%) patients, who developed VTE before starting treatment. These patients were excluded from the study (Flow diagram).

During the study period, we observed 14 (4.0%) VTE events. Deep vein thrombosis was observed in 13 patients (3.7%), and one patient (0.3%) had pulmonary embolism. No visceral thromboses were observed. One event (7.1%) was fatal. In patients without prophylaxis, we documented eight events (3.2%), while six events (5.8%) were documented in patients receiving LMWH prophylaxis. The difference was not statistically significant. (P = 0.37) The data are summarized in Table 2.

Table 2
VTE events

	No prophylaxis		VTE prophylaxis		p value
	N	%	N	%	
All VTE events	8/249	3.2	6/104	5.8	0.3681
Incidental events	2/8	25.0	4/6	66.7	0.2774
Symptomatic events	6/8	75.0	2/6	33.3	
Histology					
Seminoma	1/45	2.2	1/34	2.9	1.0000
NSGCT	7/197	3.4	5/64	7.8	0.1653
Primary tumor location					
Gonadal	8/228	3.5	4/90	4.4	0.7461
Extragenadal	0/21	0.0	2/14	14.3	0.1529
IGCCG risk group					
Stage IA/B	0/34	0.0	0/4	0.0	1.0000
Good	4/135	3.0	1/57	1.8	1.0000
Intermediate	1/31	3.2	2/15	13.3	0.2444
Poor	3/49	6.1	3/28	10.7	0.6622
Chemotherapy regimen					
BEP	6/183	3.3	2/67	3.0	1.0000
Other	2/66	3.0	4/37	10.8	0.1844

Out of the fourteen VTE events, 8 events were symptomatic, and 6 events were incidental. There were two symptomatic VTE events in patients receiving LMWH prophylaxis and six symptomatic events occurred in patients without prophylaxis (75% vs 33.3%, $P = 0.28$). In patients who experienced VTE, median time to VTE was 28.5 days (15–83 days) in patients without prophylaxis and 53.5 days (1–92 days) in patients with prophylaxis (hazard ratio (HR) = 0.53, 95% CI 0.17–1.7, $P = 0.24$).

Incidence of VTE in patients without prophylaxis before 2010 was similar to incidence of VTE in subgroup of patients with prophylaxis after 2010, totally as well as in subgroup analysis based on IGCCG risk group (Supplementary Table S1).

Association between VTE prophylaxis and patients/tumor characteristics

There were 12 VTE events in patients with non-seminomatous germ cell tumors (NSGCTs) and 2 events occurred in patients with seminoma. There were no statistically significant differences in VTE incidence between patients with and without prophylaxis based on tumor histology.

Twelve VTE events (3.8%) occurred in patients with gonadal tumors. Four events (4.4%) occurred in patients with prophylaxis and eight events (3.5%) occurred in patients without prophylaxis. The difference was not statistically significant ($P = 0.75$). Two VTE events occurred in patients with extragonadal tumors. Both patients received LMWH prophylaxis. The difference was not statistically significant. (0.0% vs. 14.3%, $P = 0.15$).

Out of the fourteen VTE events, five events occurred in patients with good risk according to IGCCCG classification, three events occurred in patients with intermediate risk and 6 events occurred in patients with poor risk. Patients with intermediate or poor risk were more likely to suffer VTE event when compared to patients with good risk according to IGCCCG classification (7.3% vs 2.2%, $P = 0.02$). However, VTE incidence did not differ significantly in patients with and without prophylaxis for none of the risk groups.

Out of the fourteen patients suffering VTE events, 8 patients received bleomycin, etoposide and cisplatin (BEP), 3 patients had dose dense regimen[16], two patients received paclitaxel, bleomycin, etoposide and cisplatin and one patient was treated with etoposide and cisplatin.

In patients receiving BEP regimen, there were 2 VTE events (3.0%) in patients receiving LMWH prophylaxis and 6 events (3.3%) in patients without LMWH prophylaxis. In patients receiving chemotherapy regimen other than BEP, there were 4 events (10.8%) in patients with LMWH prophylaxis and 2 events (3.0%) in patients without prophylaxis. The difference was not statistically significant. ($p = 0.1844$)

Association between overall survival and prophylactic anticoagulation

Median follow-up of all patients was 71 months (0-224 months). Median follow-up of alive patients was 122 months (1-224 months). There were 51 deaths (14.45%) in our study population. 2- and 5-year overall survival of the study group was 87.99% (95% CI 84.49% – 91.49%) and 84.27% (95% CI 80.22% – 88.31%), respectively. There was no difference in overall survival in patients with or without prophylaxis (HR = 0.61, 95% CI 0.32–1.13; $P = 0.0784$) (Fig. 1). The results are summarized in Table 3. Patients with extragonadal GCT and patients with NSGCT histology receiving VTE prophylaxis had significantly shorter survival compared to patients without prophylaxis (HR = 0.29, 95% CI 0.08–1.12; $P = 0.0373$, HR = 0.50, 95% CI 0.25–0.99; $P = 0.0179$ respectively) (Fig. 2A and 2B). We have also observed a trend to shorter overall survival in patients receiving prophylaxis with chemotherapy regimen other than BEP (HR = 0.50, 95% CI 0.22–1.12; $P = 0.0614$).

Table 3
Overall survival

	VTE prophylaxis	N	HR	lower 95% CI	upper 95% CI	p value
All patients	0/1	249/104	0.61	0.32	1.13	0.0784
IGCCCG risk group						
Stage IA/B	0/1	34/4	0.00	0.00	0.00	0.6532
Good	0/1	135/57	1.09	0.12	9.99	0.9425
Intermediate	0/1	31/15	0.72	0.06	9.36	0.7836
Poor	0/1	49/28	0.69	0.36	1.33	0.2368
Chemotherapy regimen						
BEP	0/1	183/67	0.94	0.37	2.42	0.8975
Other	0/1	66/37	0.5	0.22	1.12	0.0614
Tumor histology						
Seminoma	0/1	45/34	0.58	0.03	10.34	0.6988
NSGCT	0/1	204/64	0.5	0.25	0.99	0.0179
Primary tumor location						
Gonadal	0/1	228/90	0.76	0.38	1.53	0.4178
Extragonadal	0/1	21/14	0.29	0.08	1.12	0.0373

We analyzed the incidence of treatment related deaths (TRD) in patients with primary extragonadal tumors and NSGCT histology based on LMWH prophylaxis. Treatment related death was defined as death during first-line chemotherapy. Patients with extragonadal tumors receiving LMWH prophylaxis had a higher incidence of TRD compared to patients without prophylaxis (21.4% vs. 0.0%, $P = 0.0556$). Patients with NSGCT histology on LMWH prophylaxis also had a higher incidence of TRD compared to patients without prophylaxis. (10.9% vs. 3.9%, $P = 0.0552$). On subgroup analysis of patients with NSGCT histology we found that this trend was driven by TRD of patients with primary extragonadal tumors.

Incidence of major bleeding during the VTE prophylaxis

In our cohort, there were 13 patients, who suffered major bleeding (grade 3–5). There were 7 patients (2.8%) received no prophylaxis and 6 patients (5.8%) received LMWH prophylaxis. The difference was not statistically significant ($P = 0.22$)

Discussion

In the present study, we examined the relationship between prophylactic anticoagulation during chemotherapy and incidence of VTE events as well as the association between prophylactic anticoagulation and overall survival of GCT patients treated with first line chemotherapy. In order to assess the effect of prophylactic anticoagulation on the incidence of VTE events, we included only events occurring during first-line chemotherapy, when patients were also receiving LMWH prophylaxis.

We have observed that most VTE events occur even before the initiation of chemotherapy. There was a 4% incidence of VTE events occurring during chemotherapy. Observed incidence of VTE events is in line with the incidences reported in the literature.[6, 8, 10, 17-19] However, there is a wide variation in the reported incidences. While the lowest reported incidence is 2%, in a different study, there was 23.7% incidence of thromboembolic events.[8, 19] A significant part of this variation is probably caused by different inclusion criteria: including arterial events, including patients with VTE events before the start of chemotherapy, and events occurring several months after chemotherapy. Small number of patients some studies may also contribute to this variability.

We have observed no significant differences in VTE incidence between patients with and without LMWH prophylaxis. While there have been several studies assessing VTE incidence and identifying VTE risk factors in GCT patients, most of them included only a small number of the study patients with LMWH prophylaxis. Solari et al. compared the incidence of thromboembolic events in patients receiving limited and extended LMWH prophylaxis. Limited prophylaxis was administered only during hospitalization. Extended prophylaxis was administered daily from the first day of the first cycle to day 21 of the last cycle of chemotherapy. They did not observe significant differences between these two groups. However, their study did not include a control group with no prophylaxis and therefore the effect of LMWH prophylaxis cannot be assessed. Paradoxically, the incidence of thromboembolic events reported in their study (23.7%) was much higher than in other studies.[19] However, arterial events were also included in their analysis. Gizzi et al also compared the VTE incidence in GCT patients with and without LMWH prophylaxis. In their study, prophylaxis was administered to a subgroup of patients with risk factors for VTE (elevated lactate dehydrogenase or high body surface area). They have observed no statistically significant difference in VTE incidence between the two groups. However, neither the type of LMWH used nor the dosing of prophylaxis are mentioned.[12]

Unexpectedly, there was a trend to shorter overall survival in our patients who received LMWH prophylaxis. On further analysis we found a significantly shorter overall survival in patients receiving LMWH prophylaxis with NSGCT histology or extragonadal tumor location.

Prospective study assessing the effect of prophylactic anticoagulation in patients with GCT receiving chemotherapy compared to no prophylaxis is lacking. However, the data available suggest that LMWH prophylaxis does not offer the expected benefits in terms of decreased incidence of VTE events in GCT patients.[12, 19] On the contrary, our data suggest that administering LMWH prophylaxis might confer a higher risk for treatment related deaths in patients with extragonadal tumors. Given the small number of

patients with extragonadal tumors included in our study and selection bias, this result is only hypothesis generating. Further research should focus on examining the possible association between LMWH and increased incidence of TRDs. In October 2019, American Society of Clinical Oncology published an updated guideline on the use of thromboprophylaxis in cancer patients. According to this guideline, hospitalized patients with active malignancy without additional risk factors may be offered pharmacologic thromboprophylaxis. However, routine use of thromboprophylaxis in cancer patients hospitalized solely for administration of chemotherapy is no longer recommended.[20]

To the best of our knowledge, this is the largest study evaluating the effect of LMWH prophylaxis on VTE incidence in GCT patients receiving chemotherapy. Our study has several limitations. First of all, LMWH prophylaxis was not random, possibly causing selection bias. It is possible that patients at higher risk for VTE were given thromboprophylaxis more frequently what could in turn obscure the effect of thromboprophylaxis. However, incidence of VTE in patients without prophylaxis before 2010 was similar to incidence of VTE in subgroup of patients with prophylaxis after 2010, totally as well as in subgroup analysis based on IGCCCG risk group (**Supplementary Table S1**). This support the conclusion of no beneficial effect of prophylaxis in GCTs patients. Secondly, the study has retrospective design. Some VTE events could have been missed as a result of incomplete medical records.

Conclusion

In conclusion in this large retrospective analysis, we showed that LMWH prophylaxis was not associated with decreased VTE incidence. Moreover, there was a higher incidence of treatment related deaths in patients with extragonadal tumor location. Taking into account these data, LMWH prophylaxis during hospitalization should not be used in GCT patients receiving chemotherapy.

Abbreviations

BEP – bleomycin, etoposide, cisplatin

CI – confidence interval

GCT – germ cell tumor

HR – hazard ratio

IGCCCG - International Germ Cell Cancer Collaborative Group

LMWH – low molecular weight heparin

NSGCT - non-seminomatous germ cell tumor

RR – relative risk

TRD – treatment related death

VTE – venous thromboembolism

Declarations

Ethics approval

The Institutional Review Board of the National Cancer Institute, Bratislava, Slovakia approved this study and granted a waiver of consent form for the collection, analysis and publication of the retrospectively obtained and anonymised data for this non-interventional study.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

Competing interests

None declared.

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Authors' contributions

NH, MCh, KR, KK, JO, PP, VDE, ZSM, JM and MM participated in the conception and design, acquisition, analysis and interpretation of data. NH drafted the article and all authors revised it critically for important intellectual content. All the authors read this manuscript and give the final approval of the version to be published.

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Figures

Figure 1

Kaplan–Meier estimates of probabilities of overall survival according to VTE prophylaxis in testicular germ cell tumor patients (n = 353), HR = 0.61, 95% CI 0.32-1.13; P = 0.0784, 0 – no prophylaxis, 1 - prophylaxis

A

B

Figure 2

A Kaplan–Meier estimates of probabilities of overall survival according to VTE prophylaxis in testicular germ cell tumor patients ($n = 268$), $HR = 0.29$, $95\% \text{ CI } 0.08 - 1.12$; $P = 0.0373$, 0 – no prophylaxis, 1 – prophylaxis. B Kaplan–Meier estimates of probabilities of overall survival according to VTE prophylaxis in testicular germ cell tumor patients ($n = 35$), $HR = 0.50$, $95\% \text{ CI } 0.25-0.99$; $P = 0.0179$, 0 – no prophylaxis, 1 – prophylaxis

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Flowdiagram.docx](#)
- [SupplementarytableS1.docx](#)