Low-molecular-weight heparin prophylaxis is not associated with decreased incidence of venous thromboembolism in testicular germ cell tumor patients receiving chemotherapy

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Venous thromboembolism (VTE), commonly occurring in patients with testicular germ cell tumors (GCTs), is associated with increased morbidity and mortality. Prophylactic anticoagulation has been shown to decrease the risk of VTE in patients with malignancies. The objective was to evaluate the effect of low-molecular-weight heparin (LMWH) prophylaxis on the incidence of VTE and outcome in patients with GCT treated with first-line chemotherapy. In this retrospective study, 353 chemotherapy-naive GCT patients were treated with first-line chemotherapy at the National Cancer Institute, Bratislava, Slovakia (2000–2017). Median follow-up was 71 months. VTE was defined as any venous thrombosis or pulmonary embolism, confirmed by imaging, occurring during first-line chemotherapy. Exclusion criteria were LMWH use before starting chemotherapy and VTE on initial staging. We observed 14 (4.0%) VTE events. No visceral thromboses were observed. The difference in VTE incidence between patients with and without prophylaxis was not statistically significant (5.8% vs. 3.2%, p=0.37). We observed a trend toward 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 a higher incidence of treatment-related deaths in patients with extragonadal GCT receiving LMWH (p=0.06). 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. Low-molecular-weight heparin prophylaxis during hospitalization should not be used routinely in patients with testicular germ cell tumors receiving chemotherapy.

Key words: testicular germ cell tumors, venous thromboembolism, low-molecular-weight heparin, prophylaxis, chemotherapy

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

Venous thromboembolism (VTE) affects approximately 10% of cancer patients [4]. The multifactorial pathophysiology is related to the type of tumor, anatomic location, patient comorbidities, type of treatment, etc. [5] Compared to patients with different types of malignancy, GCT patients have a higher incidence of VTE events [6].

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

Few studies assessed the incidence of VTE in GCT patients, and the results vary widely. Honecker et al. observed a 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 a 5% incidence of VTE after chemotherapy [6].

Several groups have focused on the identification of risk factors for VTE events in GCT patients [6, 9–12]. Weijl et al. observed an increased risk of VTE in patients with liver metastases (odds ratio (OR) = 4.9) [10]. Piketty et al. identi-

fied body surface area >1.9 m² (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 a 4% probability of having VTE, while patients with at least 1 risk factor had a 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 a lower incidence of thromboembolic events in patients receiving thromboprophylaxis than in patients without prophylaxis [12]. However, the small number of patients in each subgroup of this study makes the interpretation of the results difficult, and a larger study is needed to elucidate the relationship between thromboprophylaxis and the incidence of VTE in patients with GCT undergoing cisplatin-based chemotherapy.

The aim of this retrospective study was to evaluate the effect of low-molecular-weight heparin (LMWH) prophylaxis on the incidence of VTE events and outcomes in patients with germ cell tumors 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 a waiver of the consent form for the collection, analysis, and publication of the retrospectively obtained and anonymized data for this noninterventional study was granted. We confirm that all methods were performed in accordance with the relevant guidelines and regulations. Patients diagnosed with GCT treated with first-line/adjuvant chemotherapy at the National Cancer Institute, Bratislava, Slovakia, from January 2000 to December 2017 were eligible. Exclusion criteria were concurrent malignancy other than nonmelanoma skin cancer in the previous 5 years, previous chemotherapy, VTE diagnosed on the initial staging exam, and anticoagulation therapy (therapeutic or prophylactic) started before the initiation of first-line chemotherapy.

Definition of VTE event. VTE events were defined as any venous thrombosis or pulmonary embolism occurring between Day 1 of the first cycle of first-line chemotherapy and Day 21 of the last cycle of 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 the patients' presenting symptoms, the events were divided into symptomatic and incidental if discovered on imaging performed for a different purpose. The Khorana score was calculated as described previously [14].

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, the American Society of Clinical Oncology released clinical practice guidelines recommending prophylactic anticoagulation for hospitalized patients receiving chemotherapy [15]. Therefore, starting in January 2010, we progressively implemented prophylactic anticoagulation with LMWH (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 embolisms, confirmed by imaging modality, were classified as events. Fisher's exact test was used for statistical analysis to compare VTE events between groups with and without prophylaxis.

The primary outcome was the overall incidence of VTE events occurring during 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 the date of VTE diagnosis. The 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 the median time of observation of the study patients. Overall survival was calculated from the start date of chemotherapy to the date of the last follow-up or death of the patient. The 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 performed using NCSS 2019 statistical software [16].

Results

Patient characteristics. Our cohort included 353 patients (Figure 1). The patient characteristics are summarized in Table 1. The median age of patients at the time of enrollment was 32 years (ranging from 17 to 63 years). All patients received platinum-based chemotherapy.

VTE prophylaxis. LMWH prophylaxis was administered to 104 patients (29.5%) for the duration of hospitalization for chemotherapy (Figure 1). The majority of patients (74.3%) receiving LMWH prophylaxis after January 2010 were stage II.B or higher. Heparin assays were not routinely performed to confirm the levels.

VTE events. In our study population, most VTE events occurred even before starting chemotherapy. These patients were excluded from the study (Figure 1).

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 a pulmonary embolism. No visceral thromboses were observed (Supplementary Table S1). 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 (p=0.37). The data are summarized in Table 2. The median age of patients with and without VTE was 34 years vs. 31 years, p=0.24.

In patients who experienced VTE, the 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).
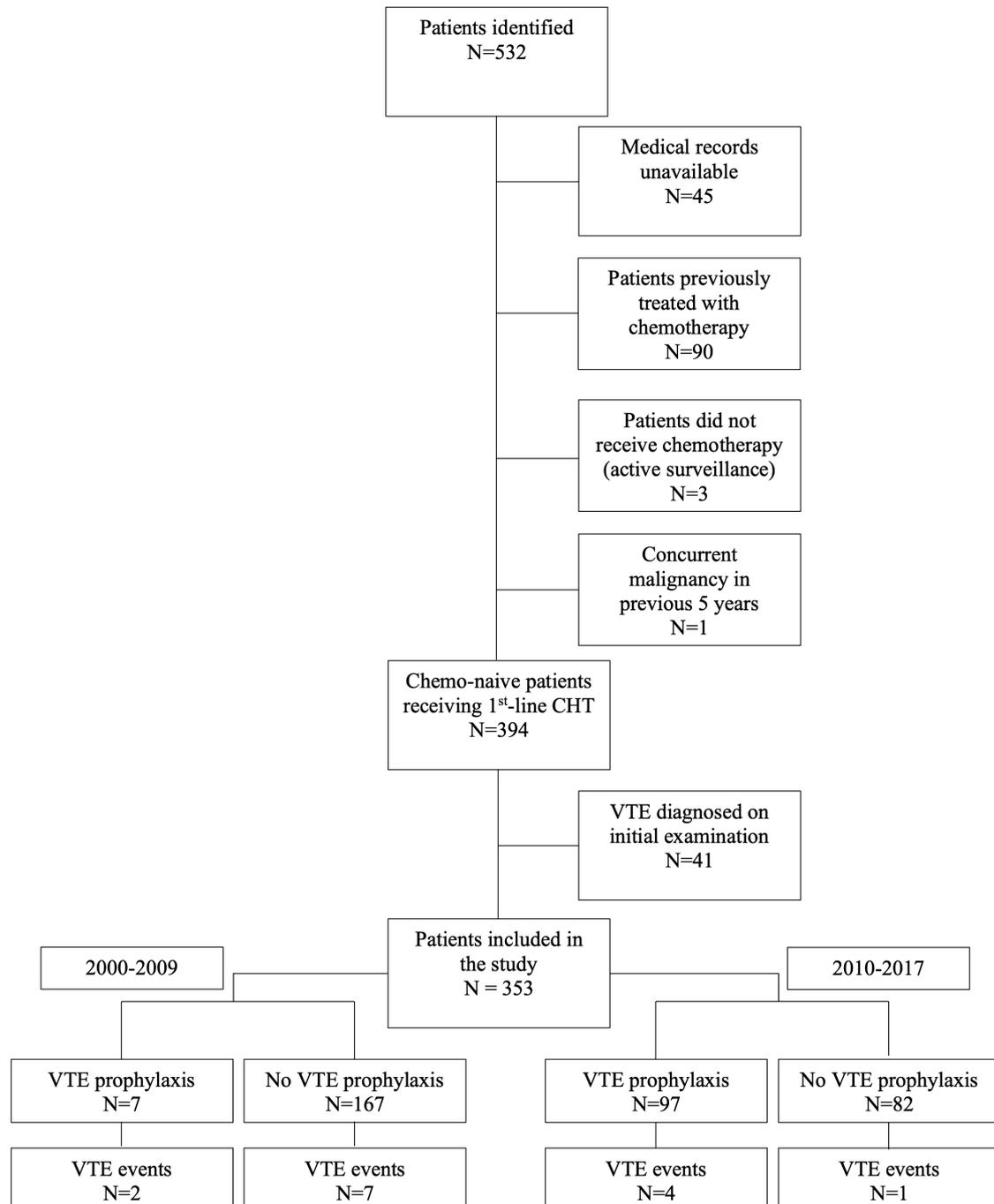
Patients identified
N=532

Medical records
unavailable
N=45

Patients previously
treated with
chemotherapy
N=90

Patients did not
receive chemotherapy
(active surveillance)
N=3

Concurrent
malignancy in
previous 5 years
N=1

Chemo-naive patients
receiving 1st-line CHT
N=394

VTE diagnosed on
initial examination
N=41

Patients included in
the study
N = 353

2000-2009

2010-2017

VTE prophylaxis
N=7

No VTE prophylaxis
N=167

VTE prophylaxis
N=97

No VTE prophylaxis
N=82

VTE events
N=2

VTE events
N=7

VTE events
N=4

VTE events
N=1

Figure 1 Flow diagram. Medical records search for patients with GCT treated between 2000 and 2017

The incidence of VTE in patients without prophylaxis before 2010 was similar to the incidence of VTE in the subgroup of patients with prophylaxis after 2010, as well as in the subgroup analysis based on the IGCCCG risk group (Supplementary Table S2).

Table 1. Patient characteristics.

	N	%
All	353	100
Histology		
Seminoma	79	22.4
NSGCT	268	75.9
Unknown	6	1.7
Primary tumor		
Gonadal	318	90.1
Extragonadal	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
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
Khorana score		
1	231	65.44
2	73	20.68
3	44	12.46
4	5	1.42
Size of retroperitoneal lymph nodes (N-stage)		
Normal (N0)	84	23.80
<2 cm (N1)	47	13.31
>2 cm <5 cm (N2)	75	21.25
>5 cm (N3)	136	38.53
Unknown	11	3.12

Association between VTE prophylaxis and patient/tumor characteristics. There were no statistically significant differences in VTE incidence between patients with and without prophylaxis based on primary tumor location or histology.

Patients with intermediate or poor-risk were more likely to suffer VTE events than patients with good risk according to the IGCCCG classification (7.3% vs. 2.2%, p=0.02). However, VTE incidence did not differ significantly in patients with and without prophylaxis for any of the risk groups. Similarly, the Khorana score and/or size of retroperitoneal lymph nodes had no impact on the effect of prophylactic anticoagulation (Table 2).

Out of the fourteen patients suffering VTE events, 8 patients received bleomycin, etoposide, and cisplatin (BEP); 3 patients had a dose-dense regimen [17]; two patients received paclitaxel, bleomycin, etoposide, and cisplatin; and one patient was treated with etoposide and cisplatin.

Association between overall survival and prophylactic anticoagulation. The median follow-up of all patients was 71 months (0–224 months). The median follow-up of living patients was 122 months (1–224 months). There were 51

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
Extragonadal	0/21	0.0	2/14	14.3	0.1529
IGCCCG 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
Khorana score					
1	6/171	3.5	1/60	1.7	0.6800
2	2/52	3.8	1/21	6.4	1.0000
3	0/22	0.0	4/22	1.8	0.1078
4	0/4	0.0	0/1	0.0	1.0000
Size of retroperitoneal lymph nodes (N-stage)					
Normal (N0)	1/70	1.4	1/12	8.3	0.2871
<2 cm (N1)	2/38	5.3	1/6	16.7	0.3907
>2 cm <5 cm (N2)	1/43	2.3	0/31	0.0	1.0000
>5 cm (N3)	3/85	3.5	4/44	9.1	0.2426

deaths (14.45%) in our study population. The 2- and 5-year overall survival rates of the study group were 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; Figure 2). The results are summarized in Table 3. Patients with extragonadal GCT and patients with NSGCT histology receiving VTE prophylaxis had significantly shorter survival than 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; Figures 3A, 3B). We also observed a trend toward shorter overall survival in patients receiving prophylaxis with chemotherapy regimens other than BEP (HR=0.50, 95% CI 0.22–1.12; p=0.0614).

We analyzed the incidence of treatment-related deaths (TRDs) in patients with primary extragonadal tumors and NSGCT histology based on LMWH prophylaxis (Supplementary Table S3). TRD was defined as a death during first-line chemotherapy. Patients with extragonadal tumors receiving LMWH prophylaxis had a higher incidence of TRD than 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 than patients without prophylaxis (10.9% vs. 3.9%, p=0.0552). In the subgroup analysis of patients with NSGCT histology, we found that this trend was driven by TRD in patients with primary extragonadal tumors.

Incidence of major bleeding during VTE prophylaxis. Thirteen patients in our cohort suffered major bleeding (grades 3–5). There were 7 patients (2.8%) who received no prophylaxis, and 6 patients (5.8%) received LMWH prophylaxis (p=0.22).

Discussion

In the present study, we examined the relationship between prophylactic anticoagulation during chemotherapy and the incidence of VTE events as well as the association between prophylactic anticoagulation and the overall survival of GCT patients treated with first-line chemotherapy. 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. Besides systemic therapy, there are at least two important factors that increase the risk of VTE in GCT patients. First, the presence of a tumor, by itself, increases the risk of thrombus formation. This is because most cancer cells have the ability to activate the coagulation system [18]. Secondly, GCTs metastasize to retroperitoneal lymph nodes (RPLN), frequently reaching a considerable size and thus causing mechanical obstruction of abdominal and pelvic veins [19]. Large RPLN size has been identified as an independent VTE risk factor in previous studies [9, 12, 20].
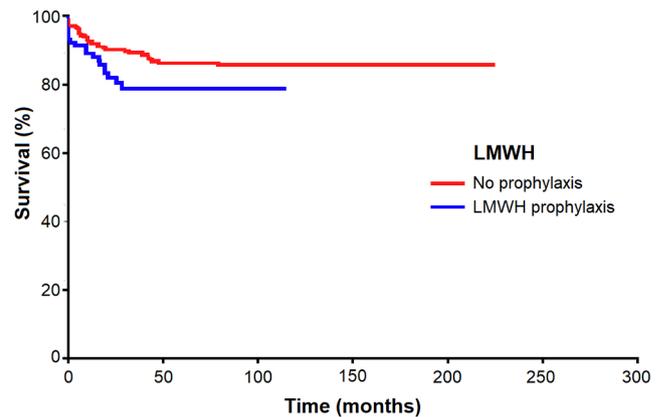

Figure 2. Kaplan-Meier estimates of probabilities of overall survival according to VTE prophylaxis in testicular germ cell tumor patients (n=353), HR=0.61, 95% CI 0.32–1.13; p=0.0784
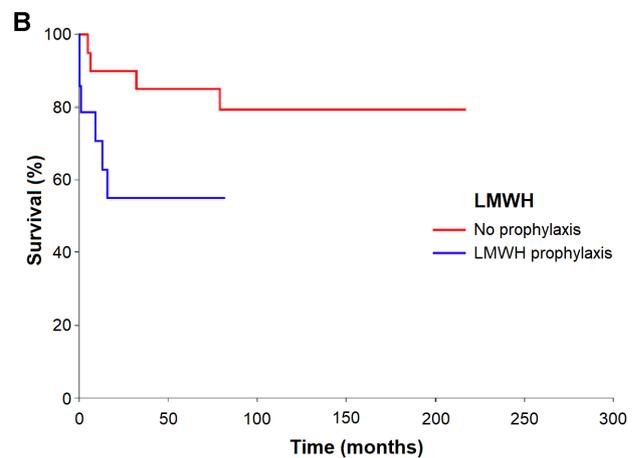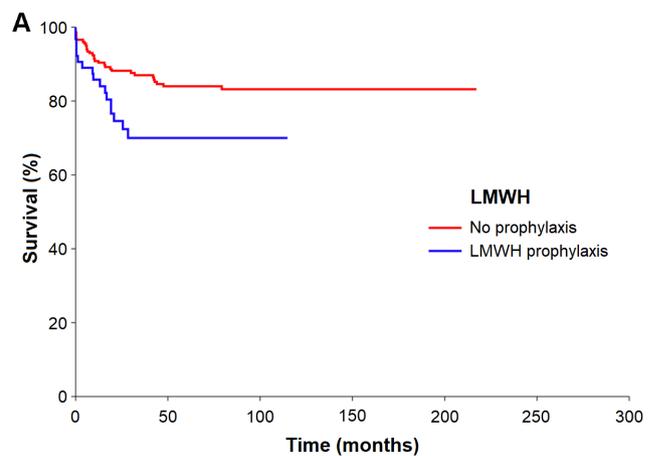

Figure 3. A) Kaplan-Meier estimates of probabilities of overall survival according to VTE prophylaxis in non-seminomatous germ cell tumor patients (n=268), HR=0.29, 95% CI 0.08–1.12; p=0.0373; B) Kaplan-Meier estimates of probabilities of overall survival according to VTE prophylaxis in extragonadal germ cell tumor patients (n=35), HR=0.50, 95% CI 0.25–0.99; p=0.0179

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
Khorana score						
1	0/1	171/60	0.83	0.25	2.76	0.7555
2	0/1	52/21	0.71	0.23	2.23	0.5272
3	0/1	22/22	0.69	0.26	1.83	0.4461
4	0/1	4/1	0.38	0.02	8.45	0.3508
Size of retroperitoneal lymph nodes (N-stage)						
Normal (N0)	0/1	71/13	0.67	0.12	3.94	0.6161
<2 cm (N1)	0/1	40/7	0.54	0.03	8.24	0.5824
>2 cm <5 cm (N2)	0/1	44/31	0.42	0.07	2.52	0.3179
>5 cm (N3)	0/1	88/48	0.88	0.38	2.00	0.7475

There was a 4% incidence of VTE events occurring during chemotherapy. The observed incidence of VTE events is in line with the incidences reported in the literature [6, 8, 10, 19, 21, 22]. However, there is a wide variation in the reported incidences [23]. While the lowest reported incidence is 2%, in a different study, there was an incidence of thromboembolic events of 23.7% [8, 22]. A significant part of this variation is probably caused by different inclusion criteria, such as including arterial events, including patients with VTE events before the start of chemotherapy, and events occurring several months after chemotherapy. The small number of patients in some studies may also contribute to this variability.

We 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 patients with GCT, most of them included only a small number of the study patients with LMWH prophylaxis. We did not observe a beneficial effect of prophylactic anticoagulation even in patients with recognized risk factors for VTE, including a high Khorana score and/or increased retroperitoneal lymph node size [14, 20].

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 Day 1 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; 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 [22]. However, arterial events were also included in their analysis. Gizzi et al. also compared the VTE incidence in patients with GCT 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 observed no statistically significant difference in VTE incidence between the two groups. However, neither the type of LMWH used nor the dosing of prophylaxis was mentioned [12].

Unexpectedly, there was a trend toward 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.

A 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 patients with GCT [12, 22]. In contrast, 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 an increased incidence of TRDs. In October 2019, the American Society of Clinical Oncology published an updated guideline on the use of thromboprophylaxis in patients with cancer. According to this guideline, hospitalized patients with active malignancy without additional risk factors may be offered pharmacologic thromboprophylaxis. However, routine use of thromboprophylaxis in patients with cancer hospitalized solely for the administration of chemotherapy is no longer recommended [24].

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

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 patients with GCT receiving chemotherapy.

Take home message. LMWH prophylaxis in GCT patients hospitalized for chemotherapy was not associated with decreased VTE incidence and therefore should not be used routinely. Moreover, LMWH prophylaxis was associated with a higher incidence of treatment-related deaths in patients with extragonadal tumor location.

Supplementary information is available in the online version of the paper.

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Low-molecular-weight heparin prophylaxis is not associated with decreased incidence of venous thromboembolism in testicular germ cell tumor patients receiving chemotherapy

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Supplementary Information

Supplementary Table S1. Thrombosis location.

Inferior vena cava	4 patients
Iliac vein	4 patients
Popliteal vein	3 patients
Subclavian vein	1 patient
Iliofemoral vein	1 patient
Pulmonary embolus	1 patient

Supplementary Table S2. VTE events before and after 2010 based on IGCCCG risk group.

	Patients without prophylaxis (before January 2010)		Patients with prophylaxis (after 2010)		p-value
	N	%	N	%	
Stage IA/B	0/17	0.0	0/4	0.0	1.0000
Good	4/84	4.8	1/56	1.8	0.6481
Intermediate	0/20	0.0	1/14	7.1	0.4118
Poor	3/46	6.5	2/23	8.7	1.0000
Khorana score					
1	5/106	4.7	1/57	1.8	0.6659
2	2/37	5.4	1/19	5.3	1.0000
3	0/21	0.0	2/20	10.0	0.2317
4	0/3	0.0	0/1	0.0	1.0000
Size of retroperitoneal lymph nodes (N-stage)					
Normal (N0)	1/43	2.3	0/12	0.0	1.0000
<2 cm (N1)	2/24	8.3	1/6	16.7	0.5235
>2 cm <5 cm (N2)	0/25	0.0	0/30	0.0	1.0000
>5 cm (N3)	3/64	4.7	3/41	7.3	0.6798

Supplementary Table S3. Causes of treatment-related death.

Acute respiratory distress syndrome	9 patients
Septic shock	4 patients
Hemorrhagic shock	1 patient
Pulmonary embolus	1 patient
Bronchopneumonia	1 patient
Sudden cardiac death (brain metastasis)	1 patient
Unknown	2 patients