Original Study

Primary Thromboprophylaxis and the Risk of Venous Thromboembolic Events in Patients With Testicular Germ Cell Tumors Treated With Cisplatinum-Based Chemotherapy

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Abstract

This retrospective cohort study shows that patients with Testicular Germ cell tumors (TGCT) undergoing cisplatinum-based chemotherapy have a high risk of venous thromboembolism (VTE). The risk of VTE was significantly reduced with primary thromboprophylaxis. Given the low risk of bleeding in patients with TGCT, it might be worthwhile to consider thromboprophylaxis for the duration of cisplatinum-based chemotherapy.

Background: Cisplatinum-based chemotherapy is associated with an increased risk of venous thromboembolism (VTE). We hypothesized that primary thromboprophylaxis in patients with testicular germ cell tumors (GCT) undergoing cisplatinum-based chemotherapy can reduce the risk of VTE. **Patients and Methods:** In this single-center retrospective cohort study, we investigated the increased use of primary thromboprophylaxis between January 2000 and December 2021 at our institution and its effect on the risk of VTE. Patients with GCT undergoing adjuvant or curative cisplatinum-based chemotherapy were included. **Results:** Three hundred forty-six patients with GCT initiating a cisplatinum-based therapy were included in the study, of whom 122 (35%) were treated in the adjuvant and 224 (65%) in the curative setting, respectively. VTE events occurred in 49 (14.2%) patients. In univariable competing risk analysis, a higher clinical tumor stage and large retroperitoneal lymphadenopathy (RPLND >5 cm) were the strongest predictors of an elevated VTE risk (SHR for stage IIC - IIIC: 2.6 (95%CI: 5.0-24.7, $P < .001$), SHR for RPLN: 2.36 (95%CI: 1.27-4.4, $P < .007$)). The proportion of patients receiving primary thromboprophylaxis strongly increased over time and reached 100% in CS IIC-III patients from 2019 onwards. After adjusting for tumor stage, primary thromboprophylaxis was associated with a 52% relatively lower risk of VTE (SHR = 0.48, 95% CI: 0.24-0.97; $P = .032$). **Conclusion:** In this retrospective cohort study, we showed that TGCT patients undergoing cisplatinum-based chemotherapy have a lower VTE risk when receiving primary thromboprophylaxis. For the duration of chemotherapy, primary thromboprophylaxis should be considered on a risk-benefit ratio.

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Introduction

The risk of VTE is increased around 4 to 6 fold in cancer patients as compared to the general population.[1,2] In patients receiving chemotherapy the risk seems to vary, ranging from 3% to 5% in patients with early-stage cancer to 30% in those with metastatic disease.[3,4] A very high incidence of thromboembolic events in patients has been observed in cancer patients receiving cisplatinum-based chemotherapy possibly due to its effect on vascular injury and endothelial dysfunction.[5-9] Primary thromboprophylaxis is recommended for hospitalized cancer patients who have a low risk of bleeding.[10,11] For ambulatory patients with cancer receiving systemic therapy the recommendation of thromboprophaylaxis is based on risk-stratification factors like the Khorana score. High-risk outpatients with a Khorana score of 2 or higher may be offered thromboprophylaxis.[10,11] However, prospective randomized clini-

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cal trials that investigated the role of thromboprophylaxis included different cancer types and patients with testicular germ cell tumors (TGCT) have been a minority in those trials.[12-14] As has been shown by Srikanthan et al and our group, tumor stage and the presence of large retroperitoneal lymphadenopathy provide a higher discriminatory performance with respect to VTE than the Khorana score for patients with TGCT.[15,16] Since then, we have consequently assessed the risk of testicular GCT patients at our department and used primary thromboprophylaxis on basis of a risk-benefit-ratio for TGCT patients undergoing cisplatin-based chemotherapy. The aim of this study was to investigate the incidence of VTE in a large cohort of TGCT patients over a time period with a consequent increase of thromboprophylaxis and its effect on VTE risk.

Patients and Methods

In this single-center cohort study consecutive patients with histologically confirmed TGCT, presenting to the Division of Oncology at the Medical University of Graz between January 2000 and December 2021, were identified (n = 1052). After a diagnosis of TGCT, patients were staged initially using computed tomographic (CT) scans of the abdomen, CT scan or X-ray of the chest, and postoperative tumor markers α-fetoprotein (AFP), human chorionic gonadotropin (HCG) and lactate dehydrogenase (LDH). Tumor markers within normal limits after orchiectomy and the absence of metastases on imaging defined Clinical Stage I (CSI). Patients with disseminated disease were risk-classified according to the International Germ Cell Cancer Collaborative group (IGCCCG).[17,18] Follow-up data were retrieved until January 2022. Follow up investigations at our center were performed according to a local protocol and were adapted in 2007 and 2012 according to recent publications.[19,20] Electronic and paper medical records of all 1052 consecutive TGCT patients were retrospectively reviewed and thromboembolic events were documented in our in-house administrative system. Eligible events were symptomatic or incidental deep vein thrombosis (DVT), visceral thrombosis, and pulmonary embolism (PE). Occurrence of VTE had to be confirmed by objective methods, such as angiography, venous Doppler ultrasound, magnetic resonance imaging, computed tomography, ventilation/perfusion scan, and were adjudicated by an independent panel of local experts. Three hundred forty-six out of these 1052 patients received cisplatin-based chemotherapy as adjuvant or curative treatment and were included for further analysis (Supplementary Figure 1). Fourteen patients had a VTE event leading to the diagnosis of testicular cancer and were subsequently not counted as VTE events in this analysis. This study was approved by the Institutional Review Board of the Medical University of Graz (No. 26-196 ex 13/1).

Statistical Methods

All statistical analyses were performed with Stata 17.0 (Windows version, Stata Corp., Houston, TX). Continuous variables were reported as medians [25th-75th percentile], and count data as absolute frequencies (%). The distribution of variables between the 2 groups were compared with rank-sum tests, χ2-tests, and Fisher's exact tests, as appropriate. For time-to-VTE analyses, the date of chemotherapy initiation (either in the adjuvant or curative setting) was the baseline date. Risks of VTE were computed with 1-Kaplan-Meier estimators and competing risk cumulative incidence estimators, treating death-from-any-cause as the competing event. Comparisons of VTE risk between patients with and without primary thromboprophylaxis were performed with log-rank tests, log-rank tests stratified for clinical stage, and adjusted Wald tests. VTE risk was modeled in the uni- and multivariable setting with Fine & Gray competing risk regression models. To gauge whether the association between primary thromboprophylaxis and VTE risk may be modified by clinical stage, interactions between thromboprophylaxis and clinical stage were fitted within a Fine & Gray model, and cumulative VTE incidences by prophylaxis and clinical stage status directly predicted from this model. Missing data are reported in Table 1, and a complete case analysis was performed.

Results

Baseline Characteristics

Three hundred forty-six patients receiving a platinum-based therapy were included in the study (Table 1), of whom 122 (35%) were treated in the adjuvant and 224 (65%) in the curative setting, respectively. As only patients treated with cisplatin-based chemotherapy were included in the study, clinical stage (CS) I seminoma as well as CS II seminoma treated with radiotherapy and patients treated with retroperitoneal lymphadenectomy only were excluded (Supplemental Data Figure 1). The cohort for the final analysis included 93 patients with metastatic seminoma, 3 patients with GCT of unknown type and 250 patients with nonseminoma of. One hundred fifty-six patients (45%) presented with CS I of whom 122 patients received adjuvant chemotherapy. Thirty-four patients with CS I were managed with active surveillance initially and received curative chemotherapy for disease relapse. One hundred ninety-patients (55%) presented with primary metastatic disease, 30% of those having CS II, 22% CS III and 3% having CS IS disease. Fifty-seven patients (17%) had bulky retroperitoneal disease larger than 5 centimeters.

VTE Events

Median follow-up for VTE was 50.6 months, and 75% and 25% of the cohort had follow-up intervals of at least 31.3 and 74.4 months, respectively. During the prespecified VTE observation period of 6 months after chemotherapy initiation, 49 patients (14%) developed VTE. These events included pulmonary embolism (PE, n = 31 (63%)), PE and deep vein thrombosis (PE+DVT, n = 8 (16%)), DVT (n = 6 (12%)), and VTE events at other sites (n = 4 (8%)). This corresponded to 1-, 2-, 3-, and 6-month cumulative VTE incidences of 2.0% (95%CI: 0.9-4.0), 8.4% (5.8-11.7), 12.3% (9.1-16.1), and 13.2% (9.9-17.1), respectively (Supplemental Data Figure 2). On average, patients who developed VTE had higher clinical tumor stages, a higher probability of stage IIC disease, and received more platinum-based chemotherapy cycles than patients who did not develop VTE, respectively. In CS I disease VTE events occurred in 9% of patients without thromboprophylaxis compared to 3% of patients with thromboprophylaxis. In CS IIC disease 50% of patients developed a VTE compared to 15% of patients with thromboprophylaxis. In CSIII 30% of patients without thromboprophylaxis suffered from a VTE event compared

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Table 1 Baseline Characteristics

Variable	Number (% Missing)	Overall (n = 346)	No VTE During Follow-up (n = 297)	VTE during Follow-up (n = 49)	P*
Demographic Characteristics					
Age	346 (0%)	35 [28-42]	35 [28-42]	34 [27-40]	.508
BMI (kg/m²)	311 (10%)	25 [23-28]	25 [23-28]	25 [22-28]	.754
Smoker or Ex-Smoker	239 (31%)	143 (60%)	128 (61%)	15 (54%)	.472
Karnofsky Index <100%	286 (17%)	39 (14%)	31 (12%)	8 (22%)	.129
Clinical variables					
Non-Seminomatous histology	343 (1%)	250 (73%)	213 (72%)	37 (77%)	.481
Clinical tumor stage	344 (1%)	/	/	/	.012
—stage IA-IB	/	156 (45%)	144 (49%)	12 (25%)	/
—stage IS	/	10 (3%)	9 (3%)	1 (2%)	/
—stage IIA–IIC	/	103 (30%)	85 (29%)	18 (38%)	/
—stage IIIA–IIIC	/	75 (22%)	58 (20%)	17 (35%)	/
RPLN(>5 cm)	340 (1%)	57 (17%)	41 (14%)	16 (33%)	.001
Primary metastatic disease	346 (0%)	190 (55%)	153 (52%)	37 (76%)	.002
Initial treatment setting	346 (0%)	/	/	/	.004
—Active Surveillance	/	34 (10%)	30 (10%)	4 (8%)	/
—Adjuvant treatment	/	122 (35%)	114 (38%)	8 (16%)	/
—Curative treatment	/	190 (55%)	153 (52%)	37 (76%)	/
IGCCCG risk stratification	190 (0%)	/	/	/	
—Good risk	/	146 (77%)	121 (79%)	25 (68%)	/
—Intermediate risk	/	20 (11%)	13 (9%)	7 (19%)	/
—Poor risk	/	24 (13%)	19 (12%)	5 (14%)	/
Type of primary chemotherapy	346 (0%)	/	/	/	.691
—PEB	/	317 (92%)	272 (92%)	45 (92%)	/
—PE	/	23 (7%)	20 (7%)	3 (6%)	/
—PEI	/	3 (1%)	3 (1%)	0 (0%)	/
—Other	/	3 (1%)	2 (1%)	1 (2%)	/
Chemotherapy cycles given	346 (0%)	/	/	/	.004
—1 cycle	/	47 (14%)	45 (15%)	2 (4%)	/
—2 cycles	/	70 (20%)	65 (22%)	5 (10%)	/
—3 cycles	/	156 (45%)	132 (44%)	24 (49%)	/
—≥4 cycles	/	73 (21%)	55 (19%)	18 (37%)	/

IGCCCG, International Germ Cell Cancer Collaborative Group.

Figure 1 Proportion of patients with primary thromboprophylaxis during the inclusion period – Distribution by clinical stage.

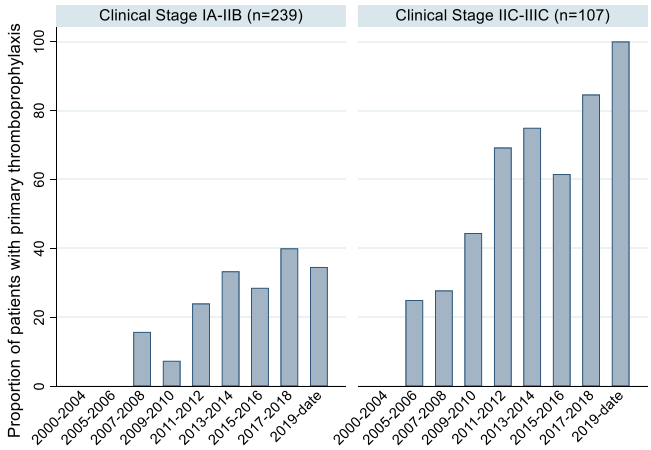
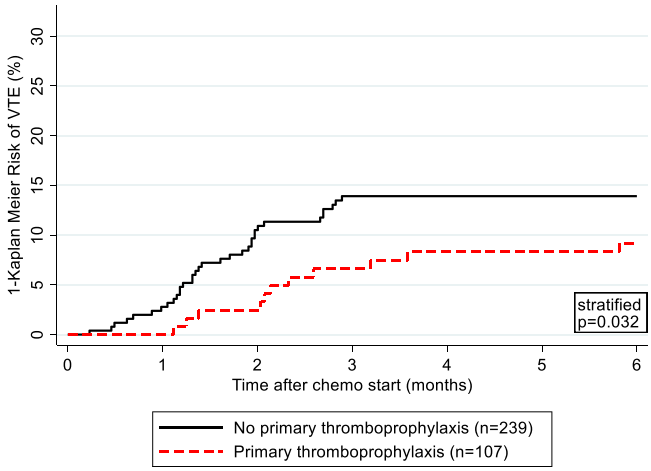


Figure 2 Primary thromboprophylaxis and risk of VTE in patients with TGCT undergoing platinum-based therapy. Data represent 1-Kaplan-Meier estimtators and a log-rank test stratified by clinical tumor stage (IA-IIB vs. IIC-IIIC).



to 13% of patients with thromboprophylaxis. Only in CS IS-IIB disease more, VTE events happened in the group with thromboprophylaxis (Supplemental Data Table 1).

Primary Thromboprophylaxis

One hundred seven patients (31%) received primary thromboprophylaxis (Table 2), of whom n = 106 (99%) received a low-molecular-weight heparin (LMWH) and n = 1 (1%) received a direct oral anticoagulant (DOAC). LMWH doses were prophylactic in n = 87 patients, semitherapeutic in n = 11 patients, and unknown in n = 8 patients, respectively. The proportion of patients receiving primary thromboprophylaxis strongly increased over time ($P < .0001$) in both patients with and without CS IIC-III disease (P for interaction= .104) and reached 35% in CS IA-IIB patients and 100% in CS IIC-III patients from 2019 onward (Figure 1). On average, patients receiving primary thromboprophylaxis had lower Karnofsky indices, higher clinical tumor stages, were more likely to have primary metastatic disease, were less likely to have IGCCCG good-risk disease, and received more chemotherapy cycles in primary platinum-based treatment (Table 2). The strongest predictor of primary thromboprophylaxis was clinical tumor stage. In detail, 54 (23%) patients with CS IA-IIB disease and 53 (50%) of patients with cS IIC-III received primary thromboprophylaxis ($P < .0001$).

Predictors of VTE Risk

Higher clinical tumor stage was the strongest univariable predictor of VTE risk (Table 3). In univariable analysis, primary throm-

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Table 2 Patient Characteristics overall and distributed by primary thromboprophylaxis

Variable	Number (% missing)	Overall (n = 346)	No Primary Thrombo-prophylaxis (n = 239)	Primary Thrombo-prophylaxis (n = 107)	P*
Demographic Characteristics					
Age	346 (0%)	35 [28-42]	34 [28-41]	37 [28-45]	.119
BMI (kg/m²)	311 (10%)	25 [23-28]	25 [23-28]	25 [23-28]	.667
Smoker or Ex-Smoker	239 (31%)	143 (60%)	108 (61%)	35 (57%)	.650
Karnofsky Index <100%	286 (17%)	39 (14%)	23 (11%)	16 (21%)	.033
Clinical variables					
Non-Seminomatous histology	343 (1%)	250 (73%)	190 (80%)	60 (57%)	<.0001
Clinical tumor stage	344 (1%)	/	/	/	<.0001
—stage IA-IB	/	156 (45%)	125 (53%)	31 (29%)	/
—stage IS	/	10 (3%)	10 (4%)	0 (0%)	/
—stage IIA–IIC	/	103 (30%)	60 (25%)	43 (41%)	/
—stage IIIA–IIIC	/	75 (22%)	43 (18%)	32 (30%)	/
RPLN(>5 cm)	340 (1%)	57 (17%)	23 (10%)	34 (33%)	<.0001
Primary metastatic disease	346 (0%)	190 (55%)	114 (48%)	76 (71%)	<.0001
Initial treatment setting	346 (0%)	/	/	/	<.0001
—Active Surveillance	/	34 (10%)	23 (10%)	11 (10%)	/
—Adjuvant treatment	/	122 (35%)	102 (43%)	20 (19%)	/
—Curative treatment	/	190 (55%)	114 (48%)	76 (71%)	/
IGCCCG risk stratification**	190 (0%)	/	/	/	.010
—Good risk	/	146 (77%)	96 (84%)	50 (66%)	/
—Intermediate risk	/	20 (11%)	7 (6%)	13 (17%)	/
—Poor risk	/	24 (13%)	11 (10%)	13 (17%)	/
Chemotherapy cycles given	346 (0%)	/	/	/	<.0001
—1 cycle	/	47 (14%)	39 (16%)	8 (7%)	/
—2 cycles	/	70 (20%)	62 (26%)	8 (8%)	/
—3 cycles	/	156 (45%)	106 (44%)	50 (47%)	/
—≥4 cycles	/	73 (21%)	32 (13%)	41 (38%)	/

IGCCCG, International Germ Cell Cancer Collaborative Group.

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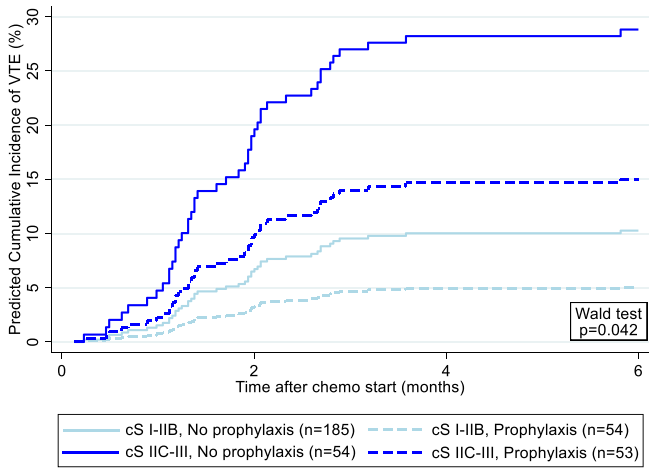
Table 3 Predictors of VTE - univariable competing risk regression

Variable	SHR	95%CI	*P*
Main study exposure			
Primary thromboprophylaxis	0.68	0.35 - 1.32	.251
Demographic characteristics			
Age (per 5 years increase)	0.97	0.85 - 1.12	.725
BMI (per 5kg/m² increase)	0.96	0.70 - 1.32	.821
Smoker/Ex-Smoker vs never smoker	0.60	0.27 - 1.31	.200
Karnofsky Index <100%	1.84	0.79 - 4.28	.156
Clinical variables			
Non-Seminomatous histology	1.30	0.65 - 2.62	.460
Clinical stage IIC–IIIC	2.60	1.45 - 4.66	.001
RPLN(>5 cm)	2.36	1.27 - 4.40	.007
Primary metastatic disease	2.24	1.15 - 4.37	.018
IGCCCG risk stratification**			
Good risk	Ref.	Ref.	Ref.
—Intermediate risk and poor risk	1.45	0.70 - 2.99	.322
Chemotherapy cycles in primary platinum-based treatment			
—1 cycle	Ref.	Ref.	Ref.
—2 cycles	1.61	0.30 - 8.59	.576
—3 cycles	3.24	0.74 - 14.18	.119
—≥4 cycles	5.03	1.13 - 22.45	.034

IGCCCG, International Germ Cell Cancer Collaborative Group.

Figure 3 Predicted risk of VTE according to primary thromboprophylaxis and clinical stage in patients with TGCT undergoing platinum-based therapy. Curves represent cumulative incidence functions that were predicted from a Fine & Gray competing risk regression model with 2 variables (primary prophylaxis and clinical stage IA-IIB vs. IIC-IIIC). The Wald-test *P*-value represents the stage-adjusted *P*-value for thromboprophylaxis (overall model *P*-value = .001). This model constrains the relative risk reduction of thromboprophylaxis to be similar in patients with stage IA-IIB and stage IIC-IIIC disease.



boprophylaxis was not associated with VTE risk (Subdistribution hazard ratio (SHR) = 0.68, 95%CI: 0.35-1.32, $P = .251$), but was strongly associated with a lower risk of VTE after adjusting for the confounding influence of clinical stage (Adjusted SHR = 0.48, 95% CI: 0.24-0.97; stage-stratified log-rank $P = .032$ (Figure 2), Wald test $P = .042$ (Figure3)). As the presence of a retroperitoneal lymph node bulk (CS IIC) and stage III were the strongest predictor of VTE, while being highly correlated with primary thromboprophylaxis, we assessed the association of primary thromboprophylaxis with VTE risk separately for patients with CS I-IIB and

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patients with CS IIC-III within an interaction analysis. Here, we did not observe that the relative association between primary thromboprophylaxis and a lower risk would be different in patients with clinical stage IA-IIB and clinical stage IIC-III disease (P for interaction = .310), although interaction-adjusted regression coefficients indicated a potentially much greater relative risk reduction with thromboprophylaxis in patients with clinical stage IIC-III disease (SHR 0.37, 95% CI 0.16-0.87, $P = .023$) vs. stage IA-IIB disease patients (SHR 0.76, 95%CI: 0.26-2.25, $P = .625$, Supplemental Data Figure 3).

Discussion

In this retrospective cohort study, we showed that TGCT patients undergoing cisplatinum-based chemotherapy have a lower VTE risk when receiving primary thromboprophylaxis. The main risk factors for VTE in TGCT patients are the clinical stage and the presence of large retroperitoneal lymphadenopathy as has been shown previously by our group and Srikanthan et al in 2015.[15,16] Since then, the use of primary thromboprophylaxis has increased significantly at our institution and has reached one hundred percent in CS IIC-IIIC disease in recent years (Figure 1). Thromboprophylaxis in cancer patients has been investigated in several trials and resulted in a relative risk reduction of 30% to 60% in VTE.[12-14] TGCT patients have been under-represented in all trials. Only three patients with TGCT were included in the AVERT trial comparing apixaban with placebo in a population consisting of 563 cancer patients.[12] Ambulatory patients with cancer who were at intermediate-to-high risk for venous thromboembolism (Khorana score ≥2) and were initiating chemotherapy were included. Apixaban resulted in a significantly lower rate of venous thromboembolism than did placebo among intermediate-to-high-risk ambulatory patients with cancer who were starting chemotherapy (4.2% vs. 10.2%; HR 0.41; $P < .001$).[12] A retrospective study by Gizzi et al suggests a similar effect of primary thromboprophylaxis on VTE in TGCT patients although this did not reach statistical significance.[21] The risk factors for stratification in this study were elevated serum lactate dehydrogenase and high body surface area (BSA). Thromboprophylaxis was associated with a numerically but not statistically significant reduced incidence of thromboembolic events (9.2% in patients with risk factors receiving LMWH vs. 16.6% in patients with risk factors not receiving LMWH, $P = .23$).[21] In our study, the incidence of VTE was 14.2% which is similar to that observed in other studies with a range from 8% to 19%.[2,22] We assessed the association of primary thromboprophylaxis with VTE risk according to clinical tumor stage because the presence of a large retroperitoneal lymphadenopathy and visceral metastases were the strongest predictors of VTE. After adjusting for the confounding influence of clinical stage, primary thromboprophylaxis was strongly associated with a 52% risk reduction of VTE ($P = .032$, Figure 2). To gauge whether the potential efficacy of primary thromboprophylaxis may be higher in patients with more advanced disease, we fitted an interaction between thromboprophylaxis and disease stage in our VTE risk models. These models did not yield statistical significance at the 5% level that the relative association between primary thromboprophylaxis and a lower risk would be different in patients with clinical stage IA-IIB and clinical stage IIC-III disease (P for interaction = .310), although interaction-adjusted regression coefficients indicated a potentially much greater relative risk reduction with thromboprophylaxis in patients with clinical stage IIC-III disease (Supplemental Data Figure 3). Primary thromboprophylaxis might increase the risk of bleeding events. We have not recorded any major bleeding complications in our patient population. However, as this is a retrospective data collection there is the possibility of missing such a bleeding event. In a retrospective analysis by Fankhauser et al the risk of bleeding in patients with testicular cancer was <1%.[23] The simulated cumulative VTE incidence from prophylactic anticoagulation for patients on or after chemotherapy translated into a number needed to treat 45 and a number needed to harm of 186.[16] Given the low risk of bleeding in patients with TGCT, it might be worthwhile to consider thromboprophylaxis in patients of all clinical stages undergoing cisplatinum based chemotherapy in the absence of risk factors for bleeding complications such as chemotherapy-induced thrombocytopenia, chorioncarcinoma histology and tumor invasion of an adjacent organ.[16,23-25] The risk of VTE increases immediately after the initiation of chemotherapy and is negligible after the end of treatment. As cisplatinum-based chemotherapy achieves high cure rates in patients with TGCT already with first-line treatment consisting of three to 4 cycles of chemotherapy, the duration of thromboprophylaxis would be limited for 2 to 3 months in most cases.[16,26-28] The major limitation of the present analysis is its retrospective data collection. However, given the low incidence of metastatic germ cell tumors, prospective randomized trials of VTE prophylaxis are unlikely to be performed. Therefore, this analysis represents the best evidence so far that primary thromboprophylaxis leads to a risk reduction of VTE in patients with testicular GCT undergoing cisplatinum-based chemotherapy.

Conclusion

TGCT patients undergoing cisplatinum-based chemotherapy have a lower VTE risk when receiving primary thromboprophylaxis. For the duration of chemotherapy, primary thromboprophylaxis should be considered on a risk-benefit ratio.

Clinical Practice Points

- Primary Thromboprophylaxis in cancer patients has been investigated in several trials and resulted in a relative risk reduction of 30-60% in VTE. TGCT patients have been under-represented in all trials. To our knowledge, this retrospective cohort study is the best evidence so far supporting primary thromboprophylaxis in TGCT patients undergoing adjuvant or curative cisplatinum-based chemotherapy.

Author contribution

AT, FP, and TB conceived and designed the study. AT, FP and TB interpreted the results. All authors collected data and contributed patients, wrote the first draft of the manuscript and agree with the manuscript's results and conclusions and ICMJE criteria for authorship read and met.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.10.005.

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