A risk benefit analysis of prophylactic anticoagulation for patients with metastatic germ cell tumours undergoing first-line chemotherapy

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Introduction In patients with metastatic germ cell tumors (mGCT) venous thromboembolic events (VTE) are frequent complications, which are not only associated with a prolonged impact on quality of life, interruption of cancer treatment or hospitalizations but also with shorter progression-free and overall survival. Given the results of recent trials, the most recent ASCO Clinical Practice Guideline Update recommends thromboprophylaxis with apixaban, rivaroxaban, or LMWH to selected high-risk ambulatory patients with cancer. Identifying patients with mGCT at a sufficiently high risk for VTE to justify prophylactic anticoagulation is challenging, as there is an associated increased risk of bleeding. We aimed to analyse the cumulative incidence and timing of VTE in mGCT patients with and without known VTE risk factors to identify patients most likely benefiting from prophylactic anticoagulation.

Methods This retrospective analysis identified men diagnosed with mGCT from 23 institutions in 11 countries treated with first-line platinum-based chemotherapy with curative intent between 1998 and 2015. Patients treated with prophylactic anticoagulation, known history of coagulopathy or previous VTE were excluded.

VTE was recorded from 90 days before initial diagnosis up to 180 days after start of chemotherapy. We performed uni- and multivariate binary regression analyses to assess the association between previously published risk factors and VTE. The number needed to treat (NNT) and number needed to harm (NNH) were simulated by assuming similar efficacy as shown in the recent randomised controlled trial AVERT or CASSINI. In brief the hazard ratios of 0.41 and 1.96 for VTE reduction and increase risk of bleeding were used to estimate the number NNT and NNH.

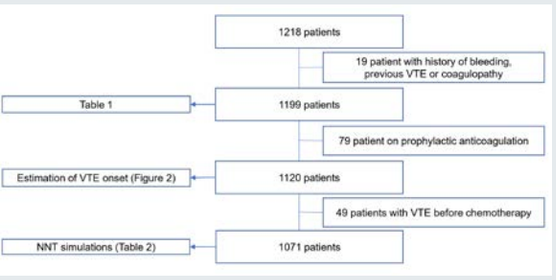

Figure 1 Patient flow diagram

Median age at diagnosis [IQR]	31 [26-38]
Primary site of GCT	
Gonadal	1111 (93%)
Extra-gonadal	84 (7%)
Missing	4 (<1%)
Histology	
Non-seminoma/Mixed	876 (73%)
Seminoma	317 (27%)
Scar	6 (<1%)
IGCCCG Prognosis	
Good	774 (65%)
Intermediate	233 (20%)
Poor	188 (15%)
Missing	4 (<1%)
Chemotherapy	
BEP	917 (76%)
EP	88 (7%)
VIP	24 (2%)
TIP	3 (<1%)
Other	85 (7%)
missing	82 (7%)
Median number of chemotherapy cycles [IQR]	3 [3-4]

Table 1 Baseline characteristics
Abbreviations: IGCCCG: International Germ Cell Cancer Collaborative Group; IQR: Interquartile range from 25-75% percentiles

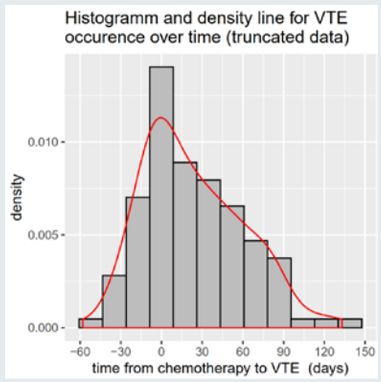

Figure 2 Histogram with density line describing the occurrence of venous thromboembolic events (VTE) before, during and after chemotherapy.

	All patients	Stratified by risk factor		
		No venous access device	Venous access device	Venous access device usage missing
Cumulative VTE incidence* 95% CI	7% (72/1071) 5-8%	5% (31/571) 4-8%	10% (23/234) 6-14%	7% (18/266) 4-10%
NNT using HR of 0.66 95% CI	45 36-56	55 40-80	31 22-47	44 29-73
NNT using HR of 0.41 95% CI	26 21-32	32 23-46	18 12-27	25 17-42

Table 2 Number needed to treat based on observed cumulative VTE incidence in 1071 patients without prophylactic anticoagulation

Abbreviations: CI: Confidence interval, HR: Hazard ration, NNT: number needed to treat, VTE: venous thromboembolic events, *defined as any deep-vein thrombosis of the lower or upper limbs, cervical or cerebral veins, pelvic and abdominal veins, pulmonary embolism during or after but not before chemotherapy. Venous access device-related VTEs were not counted as VTE in the regression or further simulation analyses.

Results Of 1,218 patients, 19 were excluded due to coagulopathy, history of VTE or bleeding (Figure 1). The resulting cohort of 1,199 men originated from 23 institutions in 11 countries with a median age of 31 years. The majority of patients had testicular non-seminomatous or mixed GCT and a good prognostic group according to IGCCCG (Table 1). In the 1120 men without prophylactic anticoagulation (Figure 1), VTE was diagnosed in 121 (11%) in the following locations: abdominal and pelvic deep vein thrombosis (DVT) in 42 (30%), pulmonary embolism in 39 (28%), lower limb DVT in 25 (18%), upper limb DVT in 11 (8%) unknown locations in 2 (1%), internal jugular thrombosis in 1 (<1%) and cerebral sinus thrombosis in 1 (<1%). Venous access device-related VTEs in 17 men were not counted as VTE. Death as a complication from VTE was reported in 9 (<1%) patients. VTE was diagnosed before chemotherapy in 49/121 (40%), during chemotherapy in 56/121 (46%) and after chemotherapy in 16/121 (13%) patients (Figure 2). After removing 49 men with VTE before chemotherapy, the cumulative VTE incidence was 72/1071 (7%). The simulated NNT (the number of patients needed to treat with prophylactic anticoagulation to prevent one VTE) would be 26 (95% 21-32) or 5(95% 36-56) depending whether the HR of the CASSINI (0.66) [3] or AVERT (0.41) [4] is used (Table 2). The only variable that remained significantly associated with VTE in a multivariable regression or after backward elimination was use of venous access devices (OR 1.8 (95% CI 0.9-3.3). In men without the risk factor venous access device, the cumulative VTE incidence was 5% leading to a NNT of 32 or 55 depending on the used HR (Table 2). In men with the risk factor venous access device, the cumulative VTE incidence was 10% leading to a NNT of 18 or 31. In 1,120 men on neither prophylactic nor full anticoagulation bleeding was reported in 6 (0.5%, 95%CI 0.02%-1%). The NNH was calculated by taking the cumulative bleeding incidence for men not treated with any anticoagulation (6/1120, 0.05%), and using the observed HR of 1.96 with DOAC prophylaxis (4) to obtain an estimated NNH of 186 (95% CI 87-506) for VTE prophylaxis in men with mGCT.

Discussion

Venous access devices double the risk of thrombosis

Avoid venous access devices

High VTE incidence before chemotherapy

Screening for VTE before chemotherapy?

All germ cell cancer patients at a *high-risk* for venous thromboembolic events

Thromboprophylaxis in all? mGCT patients before and during chemotherapy

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