



Predictors of thrombosis in testicular cancer during platinum-based chemotherapy

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Received: 29 October 2018 / Accepted: 4 December 2018 / Published online: 13 December 2018
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Abstract

Purpose To identify potential risk factors for the development of venous thromboembolic events in testicular cancer patients receiving platinum-based chemotherapy.

Methods We performed a retrospective analysis including 255 patients with testicular germ cell tumors who received platinum-based chemotherapy from 2003 to 2018 as a multi-center observational cohort study. Patient and tumor characteristics of patients with and without a thromboembolic event were analyzed.

Results 49 (19%) patients experienced a venous thromboembolic event, with the majority representing pulmonary embolism and deep venous thrombosis (47%). There were no significant differences regarding the development of a venous thromboembolic event between first- and second-line regimes. Multivariate analysis showed an increased risk for a venous thromboembolic event in patients with clinical stage \geq IIC disease (OR 2.259 [95% CI 1.105–4.618], $p=0.026$), elevated serum LDH (OR 2.162 [95% CI 1.018–4.593], $p=0.045$), febrile neutropenia (OR 2.973 [95% CI 1.363–6.487], $p=0.006$) and central venous access (OR 3.465 [95% CI 1.068–11.243], $p=0.039$). Patients suffering from a venous thromboembolic event revealed a significantly reduced overall survival ($p=0.033$) during a median follow-up of 8 months [IQR 2–18].

Conclusions 19% of all patients treated by platinum-based chemotherapy due to testicular cancer suffered from a venous thromboembolic event, associated with reduced overall survival. As a result, monitoring of cancer patients at risk as well as the improvement of patients' awareness of a thromboembolic event should thus be the main goal of their treating physicians.

Keywords Thrombosis · Germ cell tumor · Cisplatin · Chemotherapy

Abbreviations

AFP Alpha-Fetoprotein

BEP Bleomycin, etoposide, cisplatin

GCT Germ cell tumors

β -hCG Human chorionic gonadotropin

IGCCCG International germ cell cancer collaborative group

IQR Interquartile range

LDH Lactate dehydrogenase

PEI Cisplatin, etoposide, ifosfamide

PC-RPLND Post-chemotherapy retroperitoneal lymph node dissection

TIP Cisplatin, ifosfamide, paclitaxel

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00345-018-2598-7>) contains supplementary material, which is available to authorized users.

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Introduction

Testicular germ cell tumors (GCT) represent the most common solid neoplasms in young men with the highest incidence between the second and fourth decade [1]. Due to a risk-adapted interdisciplinary treatment approach including effective platinum-based chemotherapy, GCT shows excellent cure rates even in advanced stages [1]. However, chemotherapy's substantial efficacy is associated with

treatment-related toxicities like thromboembolic events (TEE) [1]. The risk of a TEE is known to be sixfold higher in cancer patients compared to their non-cancer counterparts and the second leading cause of death in cancer patients [2]. In addition, patients suffering from GCTs have a higher mortality from cardiovascular disease compared to the general population [1, 3, 4]. Despite the high number of venous or arterial thrombosis in patients receiving platinum-based chemotherapy for testicular GCT [1, 5], only few studies exist analyzing potential risk factors for TEE in these patients [3, 5–9]. A prior study identified elevated serum lactate dehydrogenase (LDH) and the presence of lymph node metastases to be predictors of TEE [5]. Furthermore, we have previously found a high tumor volume to be associated with an increased risk of a TEE during chemotherapy, which was also seen in another study [6, 10].

The aim of the present study was to assess the clinical and patient characteristics in patients receiving platinum-based chemotherapy including the incidence and localization of TEE. Another objective was to validate known predictors of venous thrombosis and identify potential new risk factors for the development of venous TEE.

Materials and methods

Study population

The testis cancer databases of the University Hospitals of Cologne and Aachen were retrospectively analyzed as a multi-center observational cohort study. 255 patients diagnosed with a malignant GCT of the testis who received a platinum-based chemotherapy between January 2003 and March 2018 have been included in the study, irrespective of tumor stage. Patients who underwent chemotherapy due to another tumor entity as well as patients with a previous history of thrombosis or a known coagulopathy were excluded from the study. The study complies with the Declaration of Helsinki and local ethics committee approval was obtained

(17–175). Informed consent was obtained from all individual participants included in the study.

Chemotherapy

All patients received a platinum-based chemotherapy with regimes being administered according to the EAU guidelines [1]. For all regimes, antiemetic prophylaxis consisted of dexamethasone 1–2 × 8 mg on day 1–5 and aprepitant 125 mg on day 1 as well as 80 mg on day 2–5. 2 mg granisetron was added in the PEI (Cisplatin, Etoposide, Ifosfamide) and TIP (Cisplatin, Ifosfamide, Paclitaxel) regime on day 1–5. For regimes with high hematotoxic potential granulocyte stimulating factor was given on day 6.

Thromboembolic events (TEE)

A TEE was defined as a venous or arterial thrombosis as well as embolism that occurred between the start of chemotherapy and 6 months after the last chemotherapy cycle and was related to the corresponding first- or second-line treatment, respectively [11]. A suspected TEE was verified by the measurement of D-Dimer, as well as radiologically via a venous doppler ultrasonography, CT scan and/or lung ventilation-perfusion scintigraphy [11] (Table 1). The treatment of a TEE consisted of a therapeutic anticoagulation with low-molecular weight heparin, phenprocoumon or rivaroxaban for at least 6 months according to the available guidelines [11, 12]. Arterial and venous TEE were analyzed separately. The three patients suffering from an arterial TEE were not included in the main analyses, but the percentage and localization of arterial TEE are displayed in Table 5.

Statistical analysis

Continuous variables were summarized as median (25th–75th%) and categorical variables as count (*n*, %). Differences in distribution of any two continuous variables were evaluated by the Mann–Whitney *U* test and statistical association of any two categorical variables by Pearson's Chi

Table 1 Patient characteristics of study population (max. *n* = 252)

Parameter	Total <i>n</i> = 252	Thrombosis <i>n</i> = 49 (19%)	No thrombosis <i>n</i> = 203 (81%)	<i>p</i> value
Age [years]	33 [26–43]	36 [27–45]	33 [26–42]	0.257
Height [cm]	182 [177–187]	182 [178–186]	182 [177–187]	0.919
Weight [kg]	82 [73–93]	83 [74–95]	82 [72–91]	0.324
BMI [kg/m ²]	25 [22–28]	25 [22–28]	24 [22–28]	0.486
BSA [m ²]	2.03 [1.90–2.17]	2.06 [1.94–2.22]	2.02 [1.90–2.16]	0.317
Elevated BSA > 1.9 m ²	144/190 (76%)	33/40 (83%)	111/150 (74%)	0.265

Continuous variables are presented as median [IQR], categorical variables are given as *n* (%)

BMI body mass index, *BSA* body surface area

squared test. We used logistic regression for the univariable and multivariable analysis of venous TEE. For multivariable modelling, missing values were multiple imputed five times (fully conditional specification with ten iterations). The corresponding regression coefficients were pooled. The final (multiple) regression model was obtained by backward stepwise elimination of variables with a p value > 0.05 ; thus, the risk of overfitting needs to be considered in interpretation [13]. Odds ratios (OR) and the corresponding 95% confidence intervals were calculated. The Kaplan–Meier method was used to estimate the overall survival distribution. All reported p values are two-sided; p values < 0.05 were considered statistically significant. Statistical calculations were done with the software SPSS Statistics (23, IBM Corp., Armonk, NY, USA).

Results

Patient and tumor characteristics

The analysis of patient characteristics revealed a higher incidence of venous TEE in patients with nonpulmonary visceral metastases (18% vs. 6%, $p = 0.019$, Table 2). Furthermore, a venous TEE was seen significantly more often in patients with clinical stage \geq IIC disease (67% vs. 44%, $p = 0.004$, Table 2) as well as extended retroperitoneal lymph node metastases \geq N2 (86% vs. 63%, $p = 0.023$, Table 2).

Serum tumor markers at diagnosis

We next analyzed the circulating tumor markers and serum testosterone levels at diagnosis (Table 3). Elevated LDH > 250 U/l at diagnosis was found significantly more often in patients with a venous TEE compared to those without a TEE (72% vs. 52%, $p = 0.018$, Table 3). In addition, an inadequate tumor marker decline was seen more often in venous TEE compared to non-TEE patients (57% vs. 32%, $p = 0.026$, Table 3).

Chemotherapy and surgical management

192 (86%) patients underwent a first-line chemotherapy according to the BEP (Bleomycin, etoposide, cisplatin) regime and 31 (14%) patients received the TIP (Cisplatin, Ifosfamide, Paclitaxel) regime as a second-line treatment (Table 4). There were no significant differences in the chemotherapy regimens and dosages between patients with and without a venous TEE (BEP 89% vs. 85%, TIP 11% vs. 15%, $p = 0.545$, Table 4). Febrile neutropenia occurred more often in patients with a venous TEE compared to patients without a TEE (33% vs. 13%, $p = 0.001$, Table 4). The majority of patients suffered from febrile neutropenia during the first

cycle of chemotherapy. All venous TEE occurred after or at the same time point of febrile neutropenia. Post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) was performed in 75 (32%) of all patients. Of these, 21 (47%) patients showed a venous TEE ($p = 0.019$, Table 4). Venous TEE occurred prior to the PC-RPLND in the majority of patients (64%). 93% of all patients received a prophylactic anticoagulation with a low-molecular-weight heparin (LMWH) during the chemotherapy treatment (Table 4). The use of thromboprophylaxis was not a predictor for venous TEE in multivariate analysis (OR 1231 [95%CI 0.326–4.646]; $p = 0.759$). Furthermore, we could not show any significant difference regarding the occurrence of a venous TEE between in the different anticoagulation regimes and dosages used in our cohort of patients (Supp. Table 1).

Localization and time point of thromboembolic events

52 (20%) patients experienced an arterial or venous TEE during or after chemotherapy (Table 5). A venous thromboembolic event occurred in 49 (94%) patients with a TEE, the majority of these patients had a pulmonary embolism plus deep venous thrombosis [23 patients (47%)] or a deep venous thrombosis alone [8 patients (17%), Table 5]. An arterial TEE occurred in 3 (6%) patients: one patient suffered from an ST-elevation myocardial infarction and two patients had a thrombosis of the popliteal artery (Table 5). Unfortunately, one patient had to undergo an amputation of the effected leg due to persistent ischemia despite timely thrombectomy. Patients who received chemotherapy via a central venous access had significantly higher numbers of venous TEE compared to patients in which chemotherapy was administered via a peripheral venous catheter (15% vs. 5%, $p = 0.011$, Table 4). The majority of venous TEE occurred during the first cycle of chemotherapy (Table 6).

Relapse and overall survival during follow-up

After a median follow-up of 8 months [IQR 2–18], relapses were detected in 49 (19%) of all patients by follow-up CT scans or rising tumor markers (Table 7). 12 (5%) patients died, 25% due to a TEE, 33% due to sepsis and 42% due to tumor progression (Table 7). Kaplan–Meier estimates revealed that patients with a venous TEE showed a significantly reduced overall survival ($p = 0.033$; Fig. 1).

Analysis of predictors for thromboembolic events

Finally, the possible predictors of a venous TEE were analyzed using a binary logistic regression model (Table 8). Multivariate analysis revealed an increased risk for venous TEE in patients with clinical stage \geq IIC disease

Table 2 Pathohistological characteristics of study population (max. $n = 252$)

Parameter	Total $n = 252$	Thrombosis $n = 49$ (19%)	No thrombosis $n = 203$ (81%)	p value
Histology				0.693
Seminoma	71/235 (30%)	15/46 (33%)	56/189 (30%)	
Non-seminoma	164/235 (70%)	31/46 (67%)	133/189 (70%)	
Subtypes of non-seminoma				
Seminoma	28 (20%)	8 (20%)	20 (19%)	1.000
Embryonal carcinoma	66 (45%)	16 (40%)	50 (47%)	0.165
Teratoma	24 (16%)	9 (22%)	15 (14%)	0.377
Yolk sac tumor	18 (12%)	6 (15%)	12 (11%)	0.708
Chorion carcinoma	11 (7%)	1 (3%)	10 (9%)	0.119
Primary tumor localization				0.847
Gonadal	238/252 (94%)	46/49 (94%)	192/203 (94.5%)	
Retroperitoneal	13/252 (5%)	3/49 (6%)	10/203 (5%)	
Mediastinal	1/252 (1%)	0	1/203 (0.5%)	
Tumor size [cm]	3.8 [2.2–5.4]	3.1 [1.9–4]	4 [2.5–6]	0.295
Vascular invasion				0.958
V0	48/79 (61%)	6/10 (60%)	42/69 (61%)	
V1	31/79 (39%)	4/10 (40%)	27/69 (39%)	
Lymphatic invasion				0.281
L0	48/74 (65%)	8/10 (80%)	40/64 (63%)	
L1	26/74 (35%)	2/10 (20%)	24/64 (37%)	
Retroperitoneal lymph nodes metastases				0.023*
N0–1	44/137 (32%)	4/28 (14%)	40/109 (37%)	
N2–3	93/137 (68%)	24/28 (86%)	69/109 (63%)	
Distant metastases				0.209
M0	163/194 (84%)	29/38 (76%)	134/156 (86%)	
M1	33/194 (16%)	9/38 (24%)	24/156 (14%)	
Nonpulmonary visceral metastases	17/194 (9%)	7/38 (18%)	10/156 (6%)	0.019*
Clinical stage				0.007*
I	66/242 (28%)	5/49 (10%)	61/193 (32%)	
IIA	19/242 (8%)	2/49 (4%)	17/193 (8%)	
IIB	39/242 (16%)	9/49 (18%)	30/193 (16%)	
IIC	30/242 (12%)	11/49 (23%)	19/193 (10%)	
III	88/242 (36%)	22/49 (45%)	66/193 (34%)	
Clinical stage \geq IIC	118/242 (49%)	33/49 (67%)	85 (44%)	0.004*
IGCCCG risk classification 1997 (clinical stage II–III)				0.317
Good	113/179 (63%)	26/42 (62%)	87/137 (64%)	
Intermediate	27/179 (15%)	4/42 (10%)	23/137 (17%)	
Poor	39/179 (22%)	12/42 (28%)	27/137 (19%)	

Continuous variables are presented as median [IQR], categorical variables are given as n (%)

IGCCCG International Germ Cell Cancer Collaborative Group

(OR 2.259 [95% CI 1.105–4.618], $p = 0.026$; Table 8), elevated serum LDH (OR 2.162 [95% CI 1.018–4.593], $p = 0.045$; Table 8), febrile neutropenia (OR 3.465 [95% CI 1.068–11.243], $p = 0.039$; Table 8), and a central venous access (OR 2.973 [95% CI 1.363–6.487], $p = 0.006$; Table 8).

Discussion

Malignancies and platinum-based chemotherapy in the treatment of testicular GCT are correlated with an increased risk of TEEs [1, 14, 15]. As testis cancer patients

Table 3 Serum tumor markers and testosterone levels at diagnosis (max. $n = 252$)

Parameter	Total $n = 252$	Thrombosis $n = 49$ (19%)	No thrombosis $n = 203$ (81%)	p value
Tumor markers at diagnosis				
β -hCG [U/l; standard value < 2.6 U/l]	3.8 [0.1–105.6]	7.8 [0.1–222]	3.8 [0.1–72]	0.883
AFP [ng/ml; standard value < 5.8 ng/ml]	4 [2.5–86]	3 [2–65.2]	5 [3–89.1]	0.124
LDH [U/l; standard value < 250 U/l]	274 [200–475]	292 [203–471]	266 [192–489]	0.926
Elevated tumor markers at diagnosis				
Elevated β -hCG > 2.6 U/l (U/l)	108/197 (55%)	23/42 (55 %)	85/155 (55%)	0.993
Elevated AFP > 5.8 ng/ml (ng/ml)	85/196 (43%)	17/41 (41%)	68/155 (44%)	0.782
Elevated LDH > 250 U/l (U/l)	113/201 (56%)	31/43 (72%)	82/158 (52%)	0.018*
Testosterone level at diagnosis [nmol/l; standard value 9.9–27.8 nmol/l]	16.7 [4.2–28.5]	19.8 [20]	12.7 [3.4–23.5]	0.273
Inadequate tumor marker decline	44/121 (36%)	13/23 (57%)	31/98 (32%)	0.026*

Continuous variables are presented as median [IQR], categorical variables are given as n (%)
 AFP alpha-fetoprotein, β -hCG human chorionic gonadotropin, LDH lactate dehydrogenase

Table 4 Treatment options of study population (max. $n = 252$)

Parameter	Total $n = 252$	Thrombosis $n = 49$ (19%)	No thrombosis $n = 203$ (81%)	p -value
Chemotherapy regime				0.868
BEP	192/241 (80%)	40/47 (85%)	152/194 (78%)	
TIP	31/241 (13%)	5/47 (11%)	26/194 (13%)	
PEI	6/241 (2%)	1/47 (2%)	5/194 (3%)	
EP	1/241 (1%)	0	1/194 (1%)	
High dose	4/241 (1%)	1/47 (2%)	3/194 (1%)	
Carboplatin mono	7/241 (3%)	0	7/194 (4%)	
Chemotherapy regime				0.545
Primary (BEP)	192/223 (86%)	40/45 (89%)	152/178 (85%)	
Secondary (TIP)	31/223 (14%)	5/45 (11%)	26/178 (15%)	
Number of cycles	3 [2–4]	3 [3, 4]	3 [2–4]	0.095
Dosages of chemotherapy				
Cisplatin [mg/m ²]	40 [38–43]	41 [36–45]	40 [38–43]	0.549
Etoposide [mg/m ²]	200 [190–213]	201 [186–221]	200 [190–210]	0.508
Bleomycin [mg/m ²]	30 [30]	30 [30]	30 [30]	0.565
Paclitaxel [mg/m ²]	347 [318–386]	350 [310–388]	345 [317–387]	0.234
Ifosfamide [mg/m ²]	2408 [2151–2697]	2604 [1900–3100]	2401 [2218–2693]	1.000
Carboplatin [mg/m ²]	841 [789–925]	0	841 [789–925]	0.682
Anticoagulation	193/207 (93%)	35/38 (92%)	158/169 (94%)	0.759
Febrile Neutropenia	41/247 (17%)	15/46 (33%)	26/201 (13%)	0.001*
Central venous access	16/248 (6%)	7/48 (15%)	9/200 (5%)	0.011*
Size of Lymph Nodes before RPLND [cm]	1.8 [1.1–4.1]	3.5 [1.6–4.6]	1.5 [0.8–3.2]	0.102
Post-Chemotherapy RPLND	75/234 (32%)	21/45 (47%)	54/189 (29%)	0.019*
Vital tumor in RPLND	22/66 (33%)	6/19 (32%)	16/47 (34%)	0.848

Continuous variables are presented as median [IQR], categorical variables are given as n (%)

BEP cisplatin/etoposide/bleomycin, TIP cisplatin/ifosfamide/paclitaxel, PEI cisplatin/etoposide/ifosfamide, EP cisplatin/etoposide, RPLND retroperitoneal lymph node dissection

Table 5 Localization of the thromboembolic events ($n=52$)

Localization of thrombosis	<i>N</i> [%]
Venous or arterial thromboembolic event	52/255 (20%)
Venous thromboembolic event	49/52 (94%)
Pulmonary embolism + deep venous thrombosis	23 (47%)
Deep venous thrombosis	8 (17%)
Pulmonary embolism + V. subclavia	1 (2%)
Vena cava inferior	3 (6%)
Vena brachialis	5 (10%)
Vena subclavia	4 (8%)
Vena cephalica	1 (2%)
Vena jugularis	2 (4%)
Vena poplitea	1 (2%)
Anal vein thrombosis	1 (2%)
Arterial thromboembolic event	3/52 (6%)
Popliteal artery	2 (67%)
ST-elevation myocardial infarction	1 (33%)

Categorical variables are given as n (%)

are generally young and have excellent cure rates due to the substantial efficacy of chemotherapy, the analysis of potential risk factors for the development of a TEE has become an increasing awareness in the treatment of testicular cancer [1].

Table 6 Time point of the thromboembolic events ($n=52$)

Time point	Venous thromboembolic event [$n=49$ (94%)]	Arterial thromboembolic event [$n=3$ (6%)]
During chemotherapy	28 (57%)	3 (100%)
1. cycle	11 (39%)	3 (100%)
2. cycle	9 (32%)	0
3. cycle	6 (22%)	0
4. cycle	2 (7%)	0
After chemotherapy (max. 6 months after the last cycle)	2 (4%)	0
Unknown	19 (39%)	0

Categorical variables are given as n (%)

Table 7 Follow-up of study population ($n=252$)

Parameter	Total $n=252$	Thrombosis $n=49$ (19%)	No thrombosis $n=203$ (81%)	<i>P</i> value
Relapse	49 (19%)	11 (22%)	38 (19%)	0.467
Death	12 (5%)	7 (14%)	5 (2%)	<0.001*
Cause of death				0.137
Due to thromboembolic event	3 (25%)	3 (43%)	0	
Due to sepsis	4 (33%)	1 (14%)	3 (60%)	
Due to tumor progression	5 (42%)	3 (43%)	2 (40%)	
Follow-up [months]	8 [2–18]	12 [0–27]	8 [2–15]	0.430

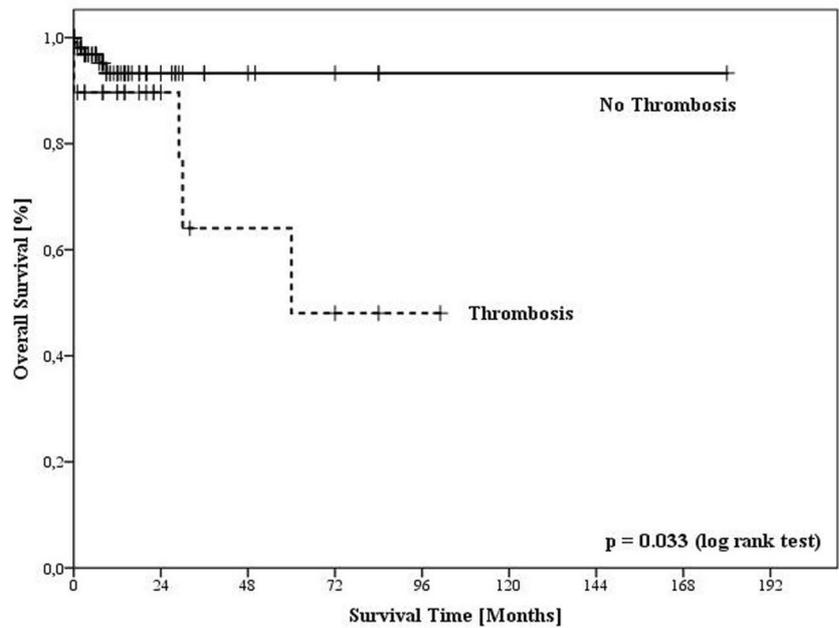
Continuous variables are presented as median [IQR], categorical variables are given as n (%)

Patients treated by second-line chemotherapy in case of progression or relapse after initial treatment with BEP consequently received higher dosages of chemotherapy compared to those treated only in the first-line setting. Although cancer itself as well as chemotherapy in testicular cancer is associated with a higher risk of TEE [1, 2], our study did not reveal any difference neither between first- and second-line chemotherapy with BEP or TIP regimen, respectively, nor in the dosages used. Regarding the development of TEE, second-line chemotherapy can thus be safely administered in the salvage situation, as it does not seem to be associated with an increased risk of venous TEE.

Furthermore, we revealed a reduced overall survival in patients with a venous TEE. The most frequent cause of mortality in our patient cohort suffering from venous TEE was thrombosis and tumor progression. A prior study identified thrombosis accounting for 9% of cancer-related deaths during chemotherapy [16]. Congruently, venous TEE was associated with an increased mortality in prostate cancer patients showing a hazard ratio of 6.89 [17]. Nevertheless, a better understanding of the mechanism responsible for the association between tumor biology and the development of TEE is warranted.

Prior studies have identified several risk factors for the development of TEE in the past decades [3, 5, 6, 8, 18, 19]. Recent studies found an elevated serum LDH to be a

Fig. 1 Kaplan–Meier estimates for overall survival of study population comparing patients with and without a venous thromboembolic event ($n = 139$)



Number at risk

Thrombosis	29	7	4	2	0	0	0	0	0
No Thrombosis	110	14	5	3	1	1	1	1	0

Number of events

Thrombosis	0	3	5	6					
No Thrombosis	0	5							

significant risk factor [3, 5, 18]. In accordance, 72% of our patients with a venous TEE showed an elevated serum LDH which was an independent risk factor for venous TEE in multivariate analysis. Thus, the level of serum LDH might not only be related to the prognosis of advanced GCTs according to the IGCCCG risk classification, but also predict the occurrence of TEE [20]. In contrast to the other tumor markers, AFP and β -hCG, LDH can be measured as a surrogate for tissue damage. However, it remains still unclear whether the destroyed cells or LDH itself are potentially associated with procoagulant factors and, therefore, responsible for an increased risk of TEE.

Furthermore, prior studies showed the presence of enlarged lymph nodes to be a risk factor for the development of TEE in platinum-based chemotherapy patients with GCTs [5, 10, 18, 19]. In addition, we have previously demonstrated that a clinical stage \geq IIC is associated with an increased risk of a venous TEE during chemotherapy [6]. The present study strongly supports these findings as multivariate analysis found clinical stage \geq IIC to be an independent risk factor for TEE. A possible explanation for a high tumor load correlated with the development of a TEE might be the compression of retroperitoneal and femoral vessels. In line with these findings, we showed that PC-RPLND was associated with the occurrence of venous TEE. As PC-RPLND is

performed only in case of persisting residual tumors > 1 cm after chemotherapy [1], these findings corroborate with the fact that a high tumor load, characterised by clinical stage \geq IIC, was shown to be an independent predictor of a venous TEE.

Moreover, febrile neutropenia was identified as an independent risk factor for venous TEE, which was underlined by a prior study [21]. TEE was recently reported to occur in 7.98% of all hospitalized adult cancer patients with febrile neutropenia including testicular cancer patients with an increasing incidence from 1995 to 2002 [22]. Another study identified multiple neutropenic episodes as a risk factor for TEE recurrence [23]. Although the conditions possibly relevant to the pathogenesis of TEE in patients suffering from febrile neutropenia are not fully understood yet, one reason might be the frequently discussed thrombogenic potential of hematopoietic growth factors that are commonly administered to patients with febrile neutropenia [22]. The majority of patients suffered from a febrile neutropenia in the first cycle of chemotherapy and all venous TEE occurred after or at the same time in our study. Thus, focused screening for TEE is warranted in patients with a febrile neutropenia.

Although the majority of venous TEE occurred as pulmonary embolism or deep venous thrombosis in our study, venous thrombosis was also seen in the upper extremities.

Table 8 Univariate and multivariate logistic regression analysis evaluating risk factors for a thromboembolic event (max. $n = 252$)

Parameter	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI of OR	<i>P</i> -value	Odds ratio	95% CI of OR	<i>P</i> -value
Age [years]	1.018	0.991–1.044	0.190			
Height [cm]	1.001	0.958–1.046	0.971			
Weight [kg]	1.006	0.986–1.026	0.585			
BMI [kg/m ²]	1.014	0.949–1.083	0.680			
BSA [m ²] ^a	1.525	0.306–7.590	0.606			
Elevated BSA > 1.9 m ² (yes vs. no) ^a	1.656	0.768–4.048	0.268			
N-Stage (N0–1 vs. N2–3) ^a	3.478	1.126–10.745	0.030*			
Metastases (M0 vs. M1)	1.733	0.730–4.115	0.213			
Nonpulmonary visceral metastases (yes vs. no)	3.297	1.164–9.334	0.025*			
Clinical Stage \geq IIC (yes vs. no)	2.621	1.353–5.077	0.004*	2.259	1.105–4.618	0.026*
IGCCCG (1 vs. 2 vs. 3)			0.326			
IGCCCG poor prognosis (yes vs. no)	1.630	0.739–3.594	0.226			
AFP [ng/ml]	1.000	1.000–1.000	0.989			
AFP elevated (yes vs. no)	0.906	0.451–1.821	0.782			
β -hCG [U/l]	1.000	1.000–1.000	0.833			
β -hCG elevated (yes vs. no)	0.997	0.503–1.978	0.993			
LDH [U/l]	1.000	0.999–1.000	0.459			
LDH elevated (yes vs. no)	2.394	1.147–4.997	0.020*	2.162	1.018–4.593	0.045*
Inadequate tumor marker decline (yes vs. no) ^a	2.810	1.111–7.106	0.029*			
PEB vs. TIP	1.368	0.494–3.789	0.546			
PC-RPLND (yes vs. no)	2.187	1.125–4.255	0.021*			
Size of lymph nodes before PC-RPLND [cm] ^a	1.438	0.808–2.559	0.217			
Vital Tumor in PC-RPLND (Yes vs. No)	0.894	0.286–2.796	0.848			
Central venous access (yes vs. no)	3.623	1.276–10.290	0.016*	3.465	1.068–11.243	0.039*
Febrile Neutropenia (yes vs. no)	3.257	1.552–6.836	0.002*	2.973	1.363–6.487	0.006*
Relapse (yes vs. no) ^a	1.509	0.625–3.645	0.360			

CI confidence interval, OR odds ratio, BMI body mass index, BSA body surface area, IGCCCG International Germ Cell Cancer Collaborative Group, AFP alpha-fetoprotein, β -hCG human chorionic gonadotropin, LDH Lactate Dehydrogenase, PC-RPLND Post-Chemotherapy retroperitoneal lymph node dissection

^aMax. 20% missings

Several studies identified the presence of a central venous access as associated with an increased risk of thrombosis in the upper extremities, also the treatment of GCTs [18]. According to prior investigations, this high potential of TEE might be provoked by contact and irritation of vascular walls with the port material [18]. In our study, patients receiving chemotherapy via a central venous access had significantly higher numbers of venous TEE compared to the administration of chemotherapy via a peripheral venous catheter ($p = 0.011$) and was furthermore identified as an independent risk factor for venous TEE. As recommendations are still missing, we consequently favour the administration of chemotherapy via a peripheral venous catheter and use a central venous access only in case of poor peripheral venous access or previously implanted port systems.

In our study, 93% of all patients received a prophylactic anticoagulation, which is in line with the management of

thromboprophylaxis in German-speaking countries, which was analyzed using standardized questionnaire [24]. In spite of that, 19% of all GCT patients suffered from a venous TEE undergoing platinum-based chemotherapy in the present study. Furthermore, we found that prophylactic anticoagulation was not a predictor for the occurrence of venous TEE and that the anticoagulation regimes and dosages did not significantly differ between patients with and without a venous TEE. The incidence of TEE was slightly higher in our dataset compared to prior studies showing a TEE rate of 8–19% [3, 5, 8, 18, 19]. However, one prior analysis showed an even higher incidence of 23.7%, not revealing any difference in the development of TEE between an extended antithrombotic prophylaxis during the complete cycle of chemotherapy and a limited prophylaxis only during hospitalization [9]. In addition, two other prior studies confirmed that anticoagulation (dosage and duration not specified)

had no significant effect on the prevention of thrombosis [3, 18]. Consequently, an intensified anticoagulation using a half-therapeutic dose or even therapeutic-dose regimes in the course of chemotherapy should be discussed in patients with risk factors for a TEE to reduce the occurrence of a TEE. Furthermore, even newer anticoagulants, that might promise a more effective and convenient prophylaxis of TEE, could be used in these patients [25]. However, further studies including these different anticoagulation regimes are warranted.

Furthermore, patients with risk factors for a TEE should be monitored more intensively for the development of venous TEE. According to recent studies, monitoring using fibrin-related markers as D-dimer, soluble fibrin, fibrinogen and fibrin degradation products can also be performed in cancer patients [26–28]. Additionally, the PELICAN study showed that patients are not well informed about the risk factors and subsequent behavioral factors of TEE [29]. Thus, patients' awareness of TEE should be proactively improved by their treating physicians to reduce mortality and morbidity. Furthermore, a prevention program for patients at risk, also informing about further, modifiable risk factors for thrombosis such as obesity, might reduce the relatively high incidence of 19% to suffer from a venous TEE during platinum-based chemotherapy for GCTs [30].

Certainly, there are some limitations to our study. First, the retrospective study design constitutes a restricted accuracy, which is usually considered to be of lower level of evidence compared to a prospective trial. Secondly, the relatively small number of cases limits the explanatory power of the study. Therefore, additional studies with a larger patient cohort are needed in order to further extend the present findings.

Conclusions

Taken together, patients with testicular GCTs undergoing platinum-based chemotherapy are at high risk of developing a venous TEE. However, second-line chemotherapy in the salvage setting was not associated with an increased risk of venous TEE. Elevated serum LDH, clinical stage \geq IIC, a central venous access and presence of febrile neutropenia during or after chemotherapy were identified as independent risk factors for the development of venous TEE in patients with GCT. Additionally, venous TEE led to a significantly reduced overall survival in GCT patients receiving platinum-based chemotherapy. Arterial embolism is rare but can have tremendous impact, so early diagnosis and therapy are mandatory. As a result, patients at risk should be monitored more intensively by their treating physicians and patients' awareness of TEE should be proactively improved.

Authors contribution MG: manuscript editing. KG: data collection or management, data analysis. IH: manuscript editing. AH: project development, manuscript editing, supervision. MH: data analysis, manuscript editing. TN: manuscript editing. PP: project development, data collection or management, data analysis, manuscript writing/editing. DP: project development, manuscript editing, supervision. JS: manuscript editing.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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