Observational Study

Thromboembolic events in metastatic testicular cancer treated with cisplatin-based chemotherapy

Lisa B E Shields, Michael W Daniels, Nataliya Mar, Arash Rezazadeh Kalebasty

**Abstract**

**BACKGROUND**

Testicular germ cell tumor (TGCT) is the most curable solid tumor and most common cancer among men 18-39 years. While cisplatin-based chemotherapy has significantly lengthened the survival of patients with TGCT, it is associated with a high rate of thromboembolic events (TEE).

**AIM**

To summarize our single-center experience highlighting patients who were diagnosed with TGCT and received platinum-based chemotherapy, with special attention to those patients who suffered a TEE.

**METHODS**

A retrospective analysis of the medical records and imaging studies of 68 consecutive individuals who were diagnosed with TGCT and received platinum-based chemotherapy at our institution in a metropolitan community between January 1, 2014 and December 31, 2019.

**RESULTS**

A total of 19 (28%) patients experienced a TEE following orchiectomy which occurred during chemotherapy in 13 (68%) of these patients. Patients with a higher pathologic stage (stage III) were significantly ($P = 0.023$) more likely to experience a TEE compared to patients who had a lower stage. Additionally, patients who were treated with 3 cycles of bleomycin, etoposide, and cisplatin and 1 cycle of etoposide and cisplatin or 4 cycles of etoposide and cisplatin were...
INTRODUCTION

According to the American Cancer Society, approximately 9610 new cases of testicular cancer will be diagnosed in 2020 with 440 deaths [6]. One in every 250 males will develop testicular cancer during their lifetime [3]. With the emergence of cisplatin-based chemotherapy in the 1970s [3], patients with testicular cancer are able to attain a 5-year survival rate of more than 95% [8,9]. However, the risk of a thromboembolic event (TEE) poses a significant concern in this population who are usually young- and middle-aged adults without medical co-morbidities. Several factors predispose to experiencing a TEE in the testicular oncologic setting including bulky retroperitoneal disease, higher clinical stage, greater number of chemotherapy cycle, central venous catheter, cigarette smoking, and possible cannabis use, high-risk ambulatory patients with TGCT treated with cisplatin-based chemotherapy may benefit from prophylactic anticoagulation. Randomized studies to evaluate the safety and efficacy of prophylactic anticoagulants are warranted in this young patient population generally devoid of medical co-morbidities.

Core Tip: While cisplatin-based chemotherapy has significantly lengthened the survival of patients with testicular germ cell tumor, it is associated with a high rate of thromboembolic events (TEE). We analyzed 68 patients who were diagnosed with testicular germ cell tumor and received platinum-based chemotherapy. A total of 19 (28%) patients experienced a TEE following orchiectomy which occurred during chemotherapy in 13 (68%) of these patients. Patients with a higher pathologic stage (stage III) were significantly more likely to experience a TEE compared to patients with a lower stage. Randomized studies to evaluate the safety and efficacy of prophylactic anticoagulants are necessary in this young patient population generally without medical co-morbidities.

CONCLUSION

Due to numerous factors that predispose to a TEE such as large retroperitoneal disease, higher clinical stage, greater number of chemotherapy cycle, central venous catheter, cigarette smoking, and possible cannabis use, high-risk ambulatory patients with TGCT treated with cisplatin-based chemotherapy may benefit from prophylactic anticoagulation. Randomized studies to evaluate the safety and efficacy of prophylactic anticoagulants are warranted in this young patient population generally devoid of medical co-morbidities.

Key Words: Oncology; Testicular cancer; Thromboembolic; Cisplatin; Pulmonary embolism; Thromboprophylaxis

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chemotherapy and a higher bleeding risk than in patients without cancer\cite{14}.

Herein, we present 68 patients with TGCT all of whom underwent cisplatin-based chemotherapy. The factors associated with an increased risk of TEE in this patient population are discussed. An analysis of thromboprophylaxis in the ambulatory setting for patients with high-risk cancer is also presented.

**MATERIALS AND METHODS**

**Study population and data collection**

Under an Institutional Review Board-approved protocol, we reviewed the medical records and imaging studies of 68 consecutive individuals who were diagnosed with TGCT and received platinum-based chemotherapy at our Institution between January 1, 2014 and December 31, 2019. All patients in our study underwent orchietomy (without any exceptions), and the pathology was determined based on the orchietomy. Standard dosing and cycles of BEP and EP were planned to be completed unless patients experienced complications from chemotherapy. A TEE was defined as a venous or arterial complication that occurred following the patient’s orchietomy for TGCT. A TEE was confirmed by venous Doppler ultrasonography or contrasted computed tomography scans. Patients with a deep venous thrombosis (DVT) had a contrasted chest computed tomography scan at baseline to rule out pulmonary embolism (PE) and to determine the length of anticoagulation treatment. None of the patients was treated with primary thromboprophylaxis.

**Statistical analysis**

The statistical analysis was performed by stratiﬁying each metric (TEE, retroperitoneal lymph nodes (RPLN) ≥ 3.0 cm before chemotherapy, age, body mass index (BMI), cigarette smoker, marijuana use, side of orchietomy, pathologic stage, CVC, type of chemotherapy, number of chemotherapy cycles, RPLN dissection (RPLND), and recurrence after chemotherapy by those patients who experienced a TEE and by those who did not. When comparing the two groups, the Fisher’s exact test and the Mann-Whitney U-test compared binary/categorical and continuous data, respectively. All analyses were performed using R software (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

**Demographics and clinicopathologic characteristics**

The mean age of the 68 patients with TCGT at orchietomy was 31 years (16-53 years) (Table 1). The mean BMI at the first medical oncology visit following orchietomy and before the initiation of chemotherapy was 29 (18.6-58.4). A total of 35 (51%) patients were current or previous cigarette smokers, and 16 (23.5%) patients were current cannabis users.

The majority [49 (72%)] of patients were diagnosed with a non-seminoma and were pathologic stage II (Table 1). A total of 18 (26%) patients had retroperitoneal lymph nodes RPLN ≥ 3.0 cm before chemotherapy, and a slightly higher number of TCGT were on the left [35 (52%)]. Most patients were treated with 3 cycles of BEP. A total of 18 (26.5%) patients underwent a RPLND, consisting of 6 before chemotherapy and 12 afterwards. RPLND is an option prior to chemotherapy in cases of mixed germ cell tumors with negative tumor markers and evidence of retroperitoneal adenopathy. RPLND is a viable possibility especially if a teratoma is suspected, the tumor is not bulky, or if the patient prefers to avoid chemotherapy. Only 1 patient had a family history of testicular cancer, specifically, in a paternal uncle. One patient was treated with 17 fractions of 2250 cGy radiation after the orchietomy and prior to the chemotherapy.

Five patients experienced recurrent disease necessitating a second course of chemotherapy after their initial cisplatin-based chemotherapy regimen. One of these patients underwent several additional courses of chemotherapy including high dose chemotherapy with autotransplant, however, succumbed to progressive disease 5 years after his orchietomy. His death was the only one in our study.
Table 1 Characteristics of patients with testicular germ cell tumors at our Institution

| Metric                                      | Number of patients (n = 68) |
|---------------------------------------------|----------------------------|
| Demographics                                |                            |
| Mean age at orchiectomy (yr)               | 31 (16-53)                 |
| Mean BMI at 1st medical oncology visit, n (%) | 29 (18.6-58.4)            |
| Cigarette smoker or ex-smoker               | 35 (51)                    |
| Current cannabis user, n (%)                | 16 (23.5)                  |
| Clinicopathologic characteristics          |                            |
| Histology, n (%)                            |                            |
| Seminoma                                    | 19 (28)                    |
| Non-seminoma                                | 49 (72)                    |
| Pathologic stage, n (%)                     |                            |
| IA                                          | 1 (1.5)                    |
| IB                                          | 1 (1.5)                    |
| IS                                          | 6 (9)                      |
| IIA                                         | 31 (45.5)                  |
| IIB                                         | 10 (14.5)                  |
| IIC                                         | 8 (11.5)                   |
| III                                         | 1 (1.5)                    |
| IIIA                                        | 2 (3)                      |
| IIIB                                        | 4 (6)                      |
| IIIC                                        | 4 (6)                      |
| Laterality, n (%)                           |                            |
| Left                                        | 35 (52)                    |
| Right                                       | 33 (48)                    |
| RPLN ≥ 3.0 cm before chemotherapy, n (%)    |                            |
| Yes                                         | 18 (26)                    |
| No                                          | 50 (74)                    |
| Type of chemotherapy                        |                            |
| BEP                                         | 58 (85.3%)                 |
| EP                                          | 4 (5.9%)                   |
| BEP + EP                                    | 6 (8.8%)                   |
| Cycles of chemotherapy                      |                            |
| 1                                           | 1 (1.5%)                   |
| 2                                           | 3 (4.4%)                   |
| 3                                           | 49 (72.0%)                 |
| 4                                           | 13 (19.1%)                 |
| 6                                           | 1 (1.5%)                   |
| 7                                           | 1 (1.5%)                   |
| RPLND                                       |                            |
| Yes                                         | 18 (26.5%)                 |
| No                                          | 50 (73.5%)                 |
| Recurrence after initial chemotherapy       |                            |
| Yes                                         | 5 (7.4%)                   |
| No                                          | 63 (92.6%)                 |

BMI: Body mass index; BEP: Bleomycin, etoposide, and cisplatin; EP: Etoposide and cisplatin; RPLN: Retroperitoneal lymph node; RPLND: Retroperitoneal lymph node dissection.

Thromboembolic events

A total of 19 (28%) patients experienced a TEE, consisting of 8 PEs, 8 DVTs, and both a PE and DVT in 3 patients (Table 2). Six patients with a TEE had a CVC for delivering chemotherapy. Four of the DVT were peripheral inserted central catheter-line related. Two patients had infusaports, one of whom had no evidence of a fibrin sheath or
Table 2 Thromboembolic events in patients with testicular germ cell tumors who underwent cisplatin-based chemotherapy at our Institution (n = 19)

| Type/pathologic stage of testicular tumor | RPLN ≥ 3.0 cm before chemotherapy | Type/number of cycles of chemotherapy | PE/DVT | Timing of PE/DVT in relation to chemotherapy | Anticoagulant | Hospitalization |
|------------------------------------------|------------------------------------|--------------------------------------|--------|---------------------------------------------|----------------|----------------|
| Seminoma IIB                             | Yes                                | BEP (2 cycles), EP (1 cycle)         | DVT    | Same day immediately prior to Cycle 1       | Fondaparinux sodium | Yes            |
| Seminoma IIA                             | No                                 | EP (3 cycles)                        | DVT¹   | During (Cycle 1)                            | Heparin → apixaban | Yes            |
| Seminoma IIIIB                           | No                                 | EP (4 cycles)                        | PE + DVT² | 3 yr after initial chemotherapy, recurrent disease | Enoxaparin sodium | Yes            |
| Non-seminoma IIB                         | Yes                                | BEP (2 cycles)                       | DVT²   | During (Cycle 2)                            | Warfarin → enoxaparin sodium | Yes            |
| Non-seminoma IIB                         | No                                 | BEP (3 cycles)                       | PE     | During (Cycle 2)                            | Heparin → enoxaparin sodium → apixaban | Yes            |
| Non-seminoma IIC                         | Yes                                | EP (4 cycles)                        | PE + DVT | 1 wk before Cycle 1                        | Heparin (lovenox) → warfarin | Yes            |
| Non-seminoma IIA                         | No                                 | BEP (3 cycles)                       | DVT²   | During (Cycle 2)                            | Fondaparinux sodium | No             |
| Non-seminoma IIB                         | Yes                                | BEP (3 cycles)                       | PE     | During (Cycle 3)                            | Fondaparinux sodium → warfarin | No             |
| Seminoma IIA                             | No                                 | BEP (3 cycles)                       | DVT²   | During (Cycle 3)                            | None             | No             |
| Seminoma III                             | No                                 | BEP (3 cycles)                       | PE     | During (Cycle 3)                            | Enoxaparin sodium | No             |
| Non-seminoma IIIIC                       | Yes                                | BEP (4 cycles)                       | PE     | During (Cycle 4)                            | Enoxaparin sodium | No             |
| Non-seminoma IIIIC                       | Yes                                | BEP (4 cycles)                       | DVT    | During (Cycle 3)                            | Enoxaparin sodium | No             |
| Non-seminoma IIIA                        | No                                 | BEP (3 cycles)                       | PE     | During (Cycle 3)                            | Heparin → rivaroxaban | Yes            |
| Non-seminoma IIIA                        | No                                 | BEP (2 cycles)                       | PE     | During (Cycle 2)                            | Enoxaparin sodium | No             |
| Seminoma IIC                             | Yes                                | BEP (3 cycles)                       | PE     | 1 mo after chemotherapy ended               | Heparin → enoxaparin sodium | Yes            |
| Seminoma IIA                             | No                                 | BEP (3 cycles)                       | PE + DVT | During (Cycle 2)                            | Heparin → enoxaparin sodium | Yes            |
| Non-seminoma IIB                         | No                                 | BEP (3 cycles)                       | DVT    | 1 d prior to Cycle 1                        | Heparin → fondaparinux sodium | Yes            |
| Non-seminoma IIIA                        | No                                 | BEP (3 cycles)                       | PE     | 2 wk after chemotherapy ended               | Warfarin + enoxaparin sodium | No             |
| Seminoma IIC                             | Yes                                | EP (4 cycles)                        | DVT²   | During (Cycle 2)                            | Enoxaparin sodium → fondaparinux | Yes            |

¹Infusaport.
²Peripherally inserted central catheter line. PE: Pulmonary embolism; BEP: Bleomycin, etoposide, and cisplatin; DVT: Deep vein thrombosis; EP: Etoposide and cisplatin.

pericatheter thrombus detected by fluoroscopic evaluation. The other patient had a family history of thromboembolic conditions.

Eight (42%) patients were diagnosed with a seminoma, and patients were either pathologic stage II [14 (74%)] or stage III [5 (26%)] (Table 2). The RPLN were ≥ 3.0 cm before chemotherapy in 8 patients (42%). The relative proportions of TEEs by at least one type stage was significantly different from the other stages (P = 0.05) (Table 3). Patients with stage IS testicular cancer were significantly (P = 0.03) less likely to experience a TEE compared to patients who had stages II or III. Note that no patients with stage IS testicular cancer had a TEE.

Most patients were scheduled to undergo 3 cycles of BEP. The relative proportions of TEEs by at least one type of chemotherapy treatment was significantly different from the other chemotherapy types (P = 0.004) (Table 3). Patients who were treated with BEP/EP and EP were significantly 5-times (1.02-28.3, P = 0.02) more likely to experience a TEE compared to patients who were only treated with BEP.
Table 3 Comparison of metrics between patients with testicular germ cell tumors at our Institution stratified by those who experienced a thromboembolic event and those who did not

| Metric                              | No (%) | Yes (%) | P value |
|-------------------------------------|--------|---------|---------|
| n                                   | 49     | 19      |         |
| Age [mean (SD)]                     | 30.9 (7.86) | 30.79 (8.67) | 0.909 |
| BMI [mean (SD)]                     | 27.87 (6.38) | 30.22 (9.25) | 0.237 |
| Cigarette smoker = Yes (%)          | 27 (55.1) | 8 (42.1) | 0.421 |
| Marijuana use = Yes (%)             | 13 (26.5) | 3 (15.8) | 0.526 |
| Side of orchiectomy = Right (%)     | 27 (55.1) | 6 (31.6) | 0.107 |
| Pathology = Seminoma (%)            | 11 (22.4) | 8 (42.1) | 0.135 |
| Pathologic stage (%)                |        |         | 0.050 |
| I                                   | 10 (20.4) | 0 (0.0) |         |
| II                                  | 33 (67.3) | 14 (73.7) |         |
| III                                 | 6 (12.2) | 5 (26.3) |         |
| Port = Yes (%)                      | 4 (8.2) | 3 (15.8) | 0.390 |
| Type of chemotherapy (%)            |         |         |         |
| BEP X 3                             | 45 (91.8) | 13 (68.4) |         |
| BEP X 3 + EP X 1                    | 4 (8.2) | 2 (10.5) |         |
| EP X 4                              | 0 (0.0) | 4 (21.1) |         |
| RPLN ≥ 3.0 cm = Yes (%)             | 10 (20.4) | 8 (42.1) | 0.123 |
| RPLND = Yes (%)                     | 12 (24.5) | 6 (31.6) | 0.555 |
| Recurrence after chemotherapy = Yes (%) | 3 (6.1) | 2 (10.5) | 0.614 |

BME: Body mass index; BEP: Bleomycin, etoposide, and cisplatin; EP: Etoposide and cisplatin; RPLN: Retroperitoneal lymph node; RPLND: Retroperitoneal lymph node dissection.

The TEE occurred during the cisplatin-based chemotherapy in 13 (68%) patients. A total of 18 (95%) patients underwent anticoagulant therapy, and 10 (56%) patients were hospitalized for management of their TEE. Eight (42%) patients were current or ex-cigarette smokers, and 3 (16%) were current cannabis users.

One patient sustained bilateral PE and a DVT 3 years after the completion of 4 cycles of EP when he experienced recurrent testicular disease. He was hospitalized and treated with enoxaparin. This patient also experienced recurrent disease and was the sole death in our study.

DISCUSSION

Cisplatin chemotherapy has been reported to cause PE, DVT, myocardial infarction, and peripheral arterial thrombosis[11,13,16]. Several pathogenic mechanisms have been identified between cisplatin and thrombosis, including endothelial cell damage marked by increased plasma levels of Von Willebrand factor during chemotherapy, platelet activation, and up-regulation of prothrombotic factors. Lauritsen et al[17] investigated cardiovascular risk factors and disease following BEP treatment for male germ cell cancer[17]. These authors reported that patients had a more than 20-fold increased hazard ratio of venous TEE compared with the normal population which decreased to a hazard ratio of 1.4 after 10 years.

In our literature review the percentage of patients who experienced a TEE with testicular cancer ranged between 5.2% and 19%[6,13,14,19]. Most of the TEE occurred during chemotherapy[6,13,14,19]. Various risk factors for a TEE were confirmed, including retroperitoneal and supraclavicular lymph node metastases, elevated serum lactic acid dehydrogenase, higher clinical stage, CVC, high body surface area, and febrile
neutropenia. Paffenholz et al\textsuperscript{(22)} reported a significantly reduced overall survival in patients with a TEE during a median follow-up of 8 mo\textsuperscript{(23)}. The present study concurs with this finding, as the TEE occurred during the cisplatin-based chemotherapy in 13 (68\%) patients.

The Khorana score is a predictive model for chemotherapy-associated TEE and is based on the following: (1) Site of cancer; (2) Prechemotherapy platelet count 350 × 10\textsuperscript{9} /L or more; (3) Hemoglobin level less than 100 g/L or use of red cell growth factors; (4) Prechemotherapy leukocyte count more than 11 × 10\textsuperscript{9}/L; and (5) BMI 35 kg/m\textsuperscript{2} or more\textsuperscript{(24)}. The risk of TEE is 4-6-fold higher in patients than in those without, and the TEE incidence is 3%-15\% annually in cancer patients\textsuperscript{(25,26)}. The use of thromboprophylaxis to reduce the recurrence of cancer-associated TEE have been examined primarily in cancers such as breast, colorectal, lung, pancreatic, and multiple myeloma that usually affect older individuals\textsuperscript{(27-30)}.

Carrier et al\textsuperscript{(27)} determined that apixaban resulted in a significantly lower rate of venous thromboembolism (VTE) than placebo among intermediate-to-high-risk ambulatory patients with cancer who started chemotherapy\textsuperscript{(31)}. In the intention-to-treat analysis, major bleeding occurred in 10 (3.5\%) patients in the apixaban group and in 5 (1.8\%) patients in the placebo group (P = 0.046). Khorana et al\textsuperscript{(28)} concluded that high-risk ambulatory patients with metastatic cancer who were receiving chemotherapy and were treated with rivaroxaban did not have a significantly lower incidence of VTE or death due to VTE in a 180-d trial period\textsuperscript{(32)}. Despite these two large randomized phase III trials, routine prophylaxis for TEE has not been embraced by clinicians in the outpatient setting as the absolute risk reduction is small and thromboprophylaxis is associated with a heightened risk of major bleeding and high-contact care\textsuperscript{(33)}.

Of the 574 patients in Carrier and colleagues' placebo-controlled study, only 3 patients were diagnosed with testicular cancer. Khorana et al\textsuperscript{(29)}'s study of 1080 patients did not specify the number of patients with testicular cancer, however, mentioned that there were 32 cases of “genitourinary” cancers that included renal, bladder, ureteral, and testicular cancers but not prostate cancer. Young men with TGCT are generally without co-morbidities. This patient population was not represented in large trials investigating thromboprophylaxis in metastatic cancer during chemotherapy. This is largely due to inclusion and exclusion criteria based on the Khorana scoring system used in these trials.

The cisplatin-based chemotherapy used to treat TGCT often does not cause severe thrombocytopenia. A relatively short course of chemotherapy in metastatic testicular cancer often leads to a cure despite the need for ongoing systemic therapy in most other metastatic solid tumors. Additionally, the cisplatin dose in the BEP regimen is higher compared to most regimens used for non-testicular cancer. This important difference may lead to better outcomes with the use of thromboprophylaxis. TGCT possesses numerous risk factors that increase the risk for clotting including bulky retroperitoneal disease, cisplatin-based chemotherapy, cigarette smoking, and possibly marijuana use. Furthermore, the risk of bleeding in TGCT is likely to be lower compared to other types of cancers due to the shorter duration of chemotherapy in TGCT and younger patient population with better bone marrow function. These factors support further investigation into the use of thromboprophylaxis as patients receive chemotherapy for TGCT.

We propose conducting a multicenter randomized double blind placebo control trial examining the efficacy and safety of thromboprophylaxis in patients undergoing systemic treatment for metastatic TGCT. Such a trial will use a novel inclusion scoring system specific for TGCT that incorporates risk factors often encountered with this cancer. Carrier et al\textsuperscript{(22)}'s as well as Khorana et al\textsuperscript{(28)}'s studies only included patients who had 2 risk factors on the Khorana scale\textsuperscript{(22,28)}. Most of the patients who experienced a TEE in the present study would not have fulfilled the criteria for inclusion for thromboprophylaxis in these 2 trials. The new TGCT scoring system should incorporate the following risk factors: Higher pathologic stage and greater number of chemotherapy cycles as confirmed by the current study as well as elevated serum lactate dehydrogenase, CVC, large RPLN, and seminoma\textsuperscript{(6,9,16,29)}.

Several studies have reported the limited use of thromboprophylaxis in TGCT with cisplatin-based chemotherapy (Table 4). Paffenholz et al\textsuperscript{(23)} reported that 93\% of all of their TGCT received prophylactic anticoagulation which is customary in Germany\textsuperscript{(34)}. Thromboprophylaxis during chemotherapy for TGCT is not customary in the United States.

Kentucky has both the highest incidence and death rates for lung cancer in the United States\textsuperscript{(35,36)}. In 2017, a total of 24.6\% of adults in Kentucky smoked while the national average was 14.0\%\textsuperscript{(37,38)}. Cigarette smoking is a well-recognized risk factor for both atherosclerotic disease and TEE\textsuperscript{(39)}. Half of the patients in our study were either
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Table 4 Patients with testicular germ cell tumors who underwent cisplatin-based chemotherapy and experienced a thromboembolic event in the literature

| Ref.              | Number of patients | Percentage of patients with TE | Main findings |
|-------------------|--------------------|--------------------------------|---------------|
| Piketty et al[9], 2005 | 100 patients with GCT; 100 controls with various neoplasms | 19 (19%) | > All stages of TGCT; > TE: 1st day of chemo to 6 mo after; > Of 19 TEE, 14 occurred during chemotherapy, 5 after chemo; > Risk factors for TEE: High body surface area, elevated serum LDH |
| Honecker et al[6], 2013 | 193 | 22 (11%) | > All stages of TGCT; > TEE: Considered therapy-associated if occurred from start of chemotherapy to 6 wk after; > 18 (%) TEE occurred before chemotherapy; > Risk factors for TEE: Pure seminoma, retroperitoneal or supraclavicular lymph node metastases, elevated LDH, CVC |
| Bezan et al[18], 2017 | 657 | 34 (5.2%) | > All stages of TGCT; > TEE: During 1st year of follow-up; > Risk factors for TEE: Higher clinical stage and RPLN, increased number of cycles of chemotherapy |
| Tran et al[19], 2019 | 1135 | 150 (10%) | > Metastatic TGCT; > TEE: During or within 90 d of chemotherapy; > Risk factors for TEE: Large RPLN, CVC |
| Paffenholz et al[16], 2019 | 225 | 49 (19%) | > All stages of TGCT; > TEE: Start of chemotherapy to 6 mo after; > Risk factors for TEE: Higher clinical stage, elevated serum LDH, febrile neutropenia, CVC; > Patients with TEE had significantly reduced overall survival during median follow-up of 8 mo |
| Current Study, 2020 | 68 | 18 (26.5%) | > All stages of TGCT; > TEE: Following orchiectomy; > Risk factors for TEE: Higher pathologic stage, greater number of chemotherapy cycles |

TGCT: Testicular germ cell tumor; TEE: Thromboembolic event; LDH: Lactic acid dehydrogenase; RPLN: Retroperitoneal lymph node; CVC: Central venous catheter.

Current or previous cigarette smokers, and 42% of these patients experienced a TEE while undergoing cisplatin-based chemotherapy. Cannabis is the most commonly used recreation drug in the United States and has been suggested to cause myocardial infarction and ischemic stroke[30]. Only a single case of PE in a young male following heavy cannabis use has been reported[30]. It has been suggested that cannabinoids, the active component of cannabis, cause endothelial cell disruption leading to vascular thrombosis. A total of 23.5% of the patients in our study were current cannabis users, and 16% of the cannabis users suffered a TEE while undergoing chemotherapy.

Our study of TCGT offers several unique aspects that shed light on the risk factors for a TEE and educational opportunities for preventing a TEE. Our study, consisting of a single Institution in a metropolitan community in Kentucky, has a large number of patients with TCGT over a 6-year period. The high percentage (28%) of patients who experienced a TEE compared to the literature may be attributed to numerous cumulative factors leading to a hypercoagulable state that may provoke a TEE, including bulky retroperitoneal disease, higher pathologic stage, greater number of chemotherapy cycles, metastatic disease, the remarkably large number of patients who smoke cigarettes and use cannabis, high number of patients with CVC, and lack of patients who were treated with thromboprophylaxis. The limitation of the present study is its retrospective nature and limited number of patients.
Several risk factors have been identified as increasing the risk of developing VTE, including the patient’s age (> 60 years), obesity, and history of anterior VTE\[^{31}\]. The tumor’s site, histological type, and stage also elevate the risk of VTE. Pancreatic cancer is the solid tumor with the highest likelihood of VTE, while lymphoma, acute leukemia, and multiple myeloma represent hematologic malignancies that pose a strong risk of VTE. Adenocarcinomas have a higher risk of VTE compared to squamous cell carcinomas, and an advanced tumor stage increases the prospect of developing a VTE\[^{31}\]. Advanced tumor stage and use of subclavian catheters are the main risk factors for CVC-associated thrombosis\[^{32}\]. Our Institution generally does not use CVC for delivering chemotherapy in patients with TCGT. However, CVC placement may be unavoidable for patients with poor venous access or patient preference. Educating patients and providers about the thromboembolic risk of CVC may discourage them from selecting CVC as the desired route of chemotherapy infusion. Further educational opportunities with patients that may decrease the likelihood of TEE and enhance overall medical health include an emphasis on discontinuing cigarette smoking and cannabis use as well as promoting weight loss.

**CONCLUSION**

Although patients with TGCT are a relatively healthy population due to their young age, myriad risk factors such as bulky retroperitoneal disease, higher clinical stage, CVC, cigarette smoking, and cannabis use may heighten their risk of developing a TEE during cisplatin-based chemotherapy. Patients with TGCT who experience a TEE may be unable to complete the course of prescribed chemotherapy despite initiating treatment with an anticoagulant. There may be a significant increase in cost of care following a TEE, including hospital stay, potential requirement for an aggressive procedure, and need for a longer duration of anticoagulation. Patients who could not complete the course of prescribed chemotherapy due to TEE will likely need more frequent medical oncology appointments with monitoring tumor markers as well as closer follow-up imaging studies which can substantially escalate the cost of patient care. High-risk ambulatory patients with TGCT treated with cisplatin-based chemotherapy may benefit from treatment with primary prophylactic anticoagulation to mitigate the potential morbidity and mortality associated with a TEE. Multi-institutional randomized studies are warranted to evaluate the safety and efficacy of thromboprophylaxis during chemotherapy for TGCT in this young patient population.

**ARTICLE HIGHLIGHTS**

**Research background**

Cisplatin-based chemotherapy has significantly increased the survival of patients with testicular germ cell tumor (TGCT), although it is associated with a high rate of thromboembolic events (TEE).

**Research motivation**

As TGCT is the most curable solid tumor and most common cancer among men 18-39 years, we sought to evaluate our single-center experience of patients who were diagnosed with TGCT and received platinum-based chemotherapy. Patients who suffered a TEE were the primary focus of this study.

**Research objectives**

Our objective was to identify patients who were diagnosed with TGCT and received platinum-based chemotherapy, with particular attention to those patients who experienced a TEE.

**Research methods**

The medical records and imaging studies of 68 consecutive individuals who were diagnosed with TGCT and received platinum-based chemotherapy at our Institution in a metropolitan community between January 1, 2014 and December 31, 2019 were reviewed. Statistical analysis was performed by stratifying each metric (TEE, retroperitoneal lymph nodes ≥ 3.0 cm before chemotherapy, age, body mass index, cigarette smoker, marijuana use, side of orchiectomy, pathologic stage, central venous
catheter, type of chemotherapy, number of chemotherapy cycles, retroperitoneal lymph nodes dissection, and recurrence after chemotherapy by those patients who experienced a TEE and by those who did not.

**Research results**
A total of 19 (28%) patients experienced a TEE following orchiectomy which occurred during chemotherapy in 13 (68%) of these patients. Patients with a higher pathologic stage (stage III) were significantly ($P = 0.023$) more likely to experience a TEE compared to patients who had a lower stage. Patients who were treated with 3 cycles of bleomycin, etoposide, and cisplatin and 1 cycle of etoposide and cisplatin or 4 cycles of etoposide and cisplatin were significantly 5 ($P = 0.02$) times more likely to experience a TEE compared to patients who were treated with only 3 cycles of bleomycin, etoposide, and cisplatin.

**Research conclusions**
Since myriad factors predispose to a TEE such as large retroperitoneal disease, higher clinical stage, greater number of chemotherapy cycle, central venous catheter, cigarette smoking, and possible cannabis use, high-risk ambulatory patients with TGCT treated with cisplatin-based chemotherapy may benefit from prophylactic anticoagulation.

**Research perspectives**
Randomized studies to evaluate the safety and efficacy of prophylactic anticoagulants are essential in this young patient population generally lacking medical co-morbidities.

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**REFERENCES**

1. American Cancer Society. Testicular cancer. [cited February 3, 2021]. Available from: https://www.cancer.org/cancer/testicular-cancer.html
2. Abdel-Razeq H, Mansour A, Abdulaleh H, Al-Shwayat A, Makoseh M, Ibrahim M, Abunasser M, Rimawi D, Al-Rabiah A, Alfar R, Abuara A, Ibrahim A, Bawalza A, Ismael Y. Thromboembolic events in cancer patients on active treatment with cisplatin-based chemotherapy: another look! *Thromb J* 2018; 16:2 [PMID: 29507532 DOI: 10.1186/s12959-018-0161-9]
3. Einhorn LH, Donohue J. Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. *Ann Intern Med* 1977; 87:293-298 [PMID: 71004 DOI: 10.7326/0003-4819-87-3-293]
4. Adra N, Einhorn LH. Testicular cancer update. *Clin Adv Hematol Oncol* 2017; 15:386-396 [PMID: 28591093]
5. Fung C, Sesso HD, Williams AM, Kerns SL, Monahan P, Abu Zaid M, Feldman DR, Hamilton RJ, Vaughn DJ, Beard CJ, Kollmannsberger CK, Cook R, Althouse S, Ardeshir-Rouhani-Fard S, Lipshultz SE, Einhorn LH, Fossa SD, Travis LB; Platinum Study Group. Multi-Institutional Assessment of Adverse Health Outcomes Among North American Testicular Cancer Survivors After Modern Cisplatin-Based Chemotherapy. *J Clin Oncol* 2017; 35:1211-1222 [PMID: 2840972 DOI: 10.1200/JCO.2016.70.3108]
6. Honecker F, Koychev D, Luhmann AD, Langer F, Dieckmann KP, Bokemeyer C, Oechsle K. Venous thromboembolic events in germ cell cancer patients undergoing platinum-based chemotherapy. *Onkologie* 2013; 36:663-668 [PMID: 24192771 DOI: 10.1159/000355652]
7. Koga F, Yamada T, Ishimaru H, Sodaoka SI, Mizuo T. Deep vein thrombosis during chemotherapy in a patient with advanced testicular cancer: successful percutaneous thrombectomy under temporary placement of retrievable inferior vena cava filter. *Int J Urol* 2001; 8:90-93 [PMID: 11240834 DOI: 10.1046/j.1442-2042.2001.00256.x]
8. Navi BB, Howard G, Howard VI, Zhao H, Judd SE, Elkind MSV, Iadecola C, DeAngelis LM, Kanel H, Okin PM, Gilchrist S, Soliman EZ, Cushman M, Safford M, Muntnier P. The risk of arterial thromboembolic events after cancer diagnosis. *Res Pract Thromb Haemost* 2019; 3:639-651 [PMID: 31624783 DOI: 10.1002/rth2.12223]
9. Piketty AC, Fléchon A, Laplanche A, Nouyrigat E, Droz JP, Théodore C, Fizazi K. The risk of thrombo-embolic events is increased in patients with germ-cell tumours and can be predicted by serum lactate dehydrogenase and body surface area. *Br J Cancer* 2005; 93:909-914 [PMID: 16205699 DOI: 10.1038/sj.bjc.6602791]
10. Seng S, Liu Z, Chiu SK, Proverbs-Singh T, Sonpavde G, Choueiri TK, Tsao CK, Yu M, Hahn NM,
Shields LBE et al. TEE in metastatic testicular cancer

Oh WK, Galsky MD. Risk of venous thromboembolism in patients with cancer treated with Cisplatin: a systematic review and meta-analysis. *J Clin Oncol* 2012; 30: 4416-4426 [PMID: 23150697 DOI: 10.1200/JCO.2012.42.4355]

Solari L, Kröning M, Ihorst G, Drognitz K, Heinz J, Jilg CA, Schultz-Seeemann W, Engelhardt M, Waller CF. High Rates of Thromboembolic Events in Patients with Germ Cell Cancer Undergoing Cisplatin-Based Polychemotherapy. *Urol Int* 2016; 96: 399-405 [PMID: 27074038 DOI: 10.1159/000445126]

Kerns SI, Fung C, Monahan PO, Ardeshir-Rouhani-Fard S, Abu Zaid MI, Williams AM, Stump TE, Sesso HD, Feldman DR, Hamilton RJ, Vaughn DJ, Beard C, Huddart RA, Kim J, Kollmannsberger C, Sahasrabudhe DM, Cook R, Fossa SD, Einhorn LH, Travis LB; Platinum Study Group. Cumulative Burden of Morbidity Among Testicular Cancer Survivors After Standard Cisplatin-Based Chemotherapy: A Multi-Institutional Study. *J Clin Oncol* 2018; 36: 1505-1512 [PMID: 29617189 DOI: 10.1200/JCO.2017.77.0735]

International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol* 1997; 15: 594-603 [PMID: 9053482 DOI: 10.1200/JCO.1997.15.2.594]

Mulder FI, van Es N, Kraaijpoel N, Di Nisio M, Carrier M, Duggal A, Gaddh M, Garcia D, Grosso MA, Kakkar AK, Mercuri MF, Middeldorp S, Royle G, Segers A, Shrivakumar S, Verhamme P, Wang T, Weitz J, Zhang G, Büller HR, Raskob G. Edoxaban for treatment of venous thromboembolism in patient groups with different types of cancer: Results from the Hokusai VTE Cancer study. *Thromb Res* 2020; 185: 13-19 [PMID: 31733403 DOI: 10.1016/j.thromres.2019.11.007]

Ostertag BM, Mannix KA, Roberts JT, Ghani SE, Harris AL. Thromboembolic events during combination chemotherapy for germ cell malignancy. *Lancet* 1988; 2: 1086-1087 [PMID: 29033318 DOI: 10.1016/S0140-6736(88)90113-4]

Paffenholz P, Grein K, Heidegger I, Nestler T, Grabbert M, Salem J, Hellmich M, Pfister D, Heidenreich A. Predictors of thrombosis in testicular cancer during platinum-based chemotherapy. *World J Urol* 2019; 37: 1907-1916 [PMID: 30547197 DOI: 10.1007/s00345-018-2598-7]

Lauritsen J, Hansen MK, Bandak M, Kreiberg MB, Skott JW, Wagner T, Gundgaard Kier MG, Holm NV, Agerbæk M, Gupta R, Dehlendorff C, Andersen KK, Daugaard G. Cardiovascular Risk Factors and Disease After Male Germ Cell Cancer. *J Clin Oncol* 2020; 38: 584-592 [PMID: 31821065 DOI: 10.1200/JCO.2019.11.0180]

Bezan A, Posch F, Ploner F, Bauernhofer T, Pichler M, Szkandera J, Hutterer GC, Pummer K, Gary, Samonnig H, Beyer J, Winder T, Hermanns T, Fankhauser CD, Gerger A, Stotz M. Risk stratification for venous thromboembolism in patients with testicular germ cell tumors. *PLoS One* 2017; 12: e0176283 [PMID: 28430804 DOI: 10.1371/journal.pone.0176283]

Tran B, Ruiz-Morales JM, Gonzalez-Billalabeitia E, Patrikiodou A, Amir E, Seidel C, Bokemeyer C, Fankhauser C, Hermanns T, Rumyantsev A, Tryakin A, Brito M, Flechon A, Kwan EM, Cheng T, Castellano D, Garcia Del Muro X, Hamid AA, Ottaviano M, Palmieri G, Kitson R, Reid A, Heng DYC, Bedard PL. Large retroperitoneal lymphadenopathy and increased risk of venous thromboembolism in patients receiving first-line chemotherapy for metastatic germ cell tumors: A study by the global germ cell cancer group (G3). *Cancer Med* 2020; 9: 116-124 [PMID: 31715650 DOI: 10.1002/cam4.2674]

Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008; 111: 4902-4907 [PMID: 18216292 DOI: 10.1182/blood-2007-10-116327]

Mulder FI, Candeloro M, Kamphuisen PW, Di Nisio M, Bossuyt PM, Gumnain N, Smit K, Büller HR, van Es N. CAT-prediction collaborators. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. *Haematologica* 2019; 104: 1277-1287 [PMID: 30606788 DOI: 10.3324/haematol.2018.209114]

Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shihvakumar S, Schattner A, Kuruvilla S, Hill D, Spadafora S, Marquis K, Trinkaus M, Tomiak A, Lee AYY, Gross PL, Lazo-Langner A, El-Maraghi R, Goss G, Le Gal G, Stewart D, Ramsay T, Rodger M, Witham D, Wells PS; AVERT Investigators. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. *N Engl J Med* 2019; 380: 711-719 [PMID: 30511879 DOI: 10.1056/NEJMoa1814468]

McBane RD 2nd, Wysokinski WE, Le-Rademacher JG, Zemla T, Asnani A, Tafur A, Perepu U, Anderson D, Gandulabalo K, Kuzma C, Perez Botero J, Leon Ferre RA, Henkin S, Lenz CJ, Houghton DE, Vishnu P, Loprinzi CL. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. *J Thromb Haemost* 2020; 18: 411-421 [PMID: 31630479 DOI: 10.1111/jth.14662]

McBane RD 2nd, Loprinzi CL, Asnani A, Lenz CJ, Houghton D, Zemla T, Le-Rademacher JG, Wysokinski WE. Extending venous thromboembolism secondary prevention with apixaban in cancer patients: The EVE trial. *Eur J Haematol* 2020; 104: 88-96 [PMID: 31606897 DOI: 10.1111/ejh.13338]

Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, Streiff MB, Garcia DA, Liebman HA, Belani CP, O'Reilly EM, Patel JN, Yimer HA, Wildgoose P, Burton P, Vijapurkar U, Kaul S, Eikelboom J, McBane R, Bauer KA, Kuderer NM, Lyman GH; CASSINI Investigators. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. *N Engl J Med* 2019; 380: 720-728 [PMID: 30786186 DOI: 10.1056/NEJMoa1814630]

Shields LBE, Wilkett Barnes JG, Buckley C, Mikos GJ, Rogers KN, Hamm JT, Flynn JM, Hester ST,
Honaker JT. Multidisciplinary approach to low-dose CT screening for lung cancer in a metropolitan community. *Fam Pract* 2020; 37: 25-29 [PMID: 31273579 DOI: 10.1093/fampra/cmz036]

**United States Preventive Services Task Force.** Lung cancer: screening. [cited February 3, 2021]. Available from: https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/Lung-cancer-screening

**Centers for Disease Control and Prevention.** Current cigarette smoking among adults in the United States. [cited February 3, 2021]. Available from: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/

Cheng YJ, Liu ZH, Yao FJ, Zeng WT, Zheng DD, Dong YG, Wu SH. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. *PLoS Med* 2013; 10: e1001515 [PMID: 23068896 DOI: 10.1371/journal.pmed.1001515]

Salhan D, Abdulfattah O, Roy S, Kandel S, Agu C, Basunia M, Enriquez D, Quist J, Schmidt FM. Cannabis-induced VTE: is it a safe recreational drug? *Chest* 2016; 150: 909A [DOI: 10.1016/j.chest.2016.08.1009]

Khalil J, Bensaid B, Elkacemi H, Aflif M, Bensaid Y, Kebdani T, Benjaafar N. Venous thromboembolism in cancer patients: an underestimated major health problem. *World J Surg Oncol* 2015; 13: 204 [PMID: 26092573 DOI: 10.1186/s12957-015-0592-8]

Wiegering V, Schmid S, Andres O, Wirth C, Wiegering A, Meyer T, Winkler B, Schlegel PG, Eyrich M. Thrombosis as a complication of central venous access in pediatric patients with malignancies: a 5-year single-center experience. *BMC Hematol* 2014; 14: 18 [PMID: 25317335 DOI: 10.1186/2052-1839-14-18]
