REVIEW ARTICLE

Thromboembolic Events During Chemotherapy for Germ Cell Cancer: A Cohort Study and Review of the Literature

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Purpose: **To evaluate the risk of major thromboembolic complications in male germ cell cancer patients receiving cisplatin-based chemotherapy and to review the literature on this subject.**

Patients and Methods: **One hundred seventy-nine germ cell cancer patients treated between January 1979 and May 1997 in our hospital were analyzed with respect to risk factors for developing thromboembolic events, such as baseline tumor characteristics, prior tumor therapy, administration of cytostatic agents, and the use of antiemetic drugs. The patients were treated with a variety of combination chemotherapy regimens, primarily cisplatin-containing combination regimens.**

Results: **Of the 179 patients, 15 patients (8.4%) were identified who developed a total of 18 major thromboembolic complications in the time period between the start of chemotherapy and 6 weeks after administration of the last cytostatic drug in first-line treatment. Of these 18 events, three (16.7%) were arterial events, including two cerebral ischemic strokes, and 15 (83.3%) were venous thromboembolic events, including 11 pulmonary embolisms. One (5.6%) of the 18 events was fatal. Liver metastases (odds ratio, 4.9; 95% confidence interval, 1.1 to 20.8) and the administration of high doses of corticosteroids (≥ 80 mg dexamethasone per cycle; odds ratio, 3.5; 95% confidence interval, 1.2 to 10.3) as antiemetic therapy were identified as risk factors for the development of major thromboembolic complications.**

Conclusion: **Germ cell cancer patients who receive chemotherapy, in particular those who have liver metastases or receive high doses of corticosteroids, are at considerable risk of developing thromboembolic complications.**

J Clin Oncol 18:2169-2178. © 2000 by American Society of Clinical Oncology.

THE INTRODUCTION OF cisplatin-based regimens for the treatment of patients with disseminated germ cell cancer has resulted in high remission rates and much improved survival. As a larger number of germ cell cancer patients are cured and become long-term survivors, increased attention has been focused on treatment-induced organ damage. The spectrum of chemotherapy-related complications, such as cisplatin-related damage to the kidney and peripheral nerves and bleomycin-induced pulmonary fibrosis, has been well documented. However, thromboembolic complications, such as pulmonary embolism, myocardial infarction, and stroke, in relation to the chemotherapy for germ cell cancer has primarily been described in case reports,[1-19] whereas only a few studies exist concerning the incidence of thromboembolic toxicity in these patients.[20-29] The etiology of thromboembolisms is thought to be multicausal.[30] Disease and treatment-related factors, such as surgery, periods of immobilization, and the hypercoagulable state of patients with (adeno)carcinoma, have often been associated with venous thromboembolic events in cancer patients.[31-32] Several other mechanisms have been hypothesized for the occurrence of venous and arterial thrombotic complications in patients with disseminated germ cell cancer, including cisplatin-related hypomagnesemia, drug-induced damage of the vascular endothelium, and elevation of von Willebrand factor plasma levels.[33] Recently, several mutations have been described that increase the risk of venous thrombosis in general, ie, in clotting factor V (factor V 1691 G-to-A or factor V Leiden) and in prothrombin (20210 G-to-A).[34,35] Because these strong risk factors for thrombosis (three- to eight-fold increased risk) are highly prevalent in the general population (2% to 5% each),[30] we hypothesized that they contributed to the risk of thrombosis in patients receiving chemotherapy.

Recently, a number of germ cell cancer patients treated with chemotherapy in our department developed major thromboembolic events, such as cerebrovascular accidents and pulmonary embolism. This prompted us to perform a retrospective study to determine the incidence and fatality rate of thromboembolic events and to assess which disease- and treatment-related factors were associated with these life-threatening complica-

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Submitted May 10, 1999; accepted January 25, 2000.

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0732-183X/00/1810-2169

tions in young men with a high chance of being cured of malignancies. In addition, we reviewed the relevant literature, with special emphasis on risk factors.

PATIENTS AND METHODS

Treatments

The medical records of 184 consecutive male patients with germ cell cancer who underwent chemotherapy in the period between January 1979 until May 1997 in the Department of Clinical Oncology of the Leiden University Medical Center were examined. Five patients were excluded from analysis: four because their clinical records were incomplete with regard to the administered drugs, and one because he received only 2 days of chemotherapy and died 3 days later of respiratory failure due to massive pulmonary metastases. Of the remaining 179 patients, including 166 patients with primary testicular tumors and 13 patients with primary extragonadal tumors, only the thromboembolic events related to the first-line treatment were analyzed. The majority of patients received four to six cycles of intravenously (IV) administered combination chemotherapy; cycles were repeated every 21 days. Seventy-nine patients (44.1%) were treated with the combination of bleomycin, etoposide, and cisplatin and 33 (18.4%) with cisplatin, vinblastine, and bleomycin. In these schedules, cisplatin was administered during the first 2 or 5 days of each cycle, for a total dose of 100 mg/m^2 per cycle. Bleomycin was administered every week (30 IU/wk), and vinblastine (0.15 mg/kg on days 1 and 2) and etoposide during the first 3 to 5 days of each cycle, for a total etoposide dose of 500 mg/m^2 per cycle. The other patients were treated with a variety of other combination chemotherapy schedules, primarily those based on cisplatin, but 16 patients (8.9%) were treated with the cisplatin analog carboplatin.

During the period from 1979 until the end of the 1980s, a wide range of agents was used as comedication against the cisplatin-induced emesis, eg, benzamides, benzodiazepines, antihistamines, phenothiazines, and butyrophenones. After the introduction of corticosteroids and serotonin-receptor antagonists as superior antiemetic drugs, more standardized antiemetic regimens were used, in which either serotonin-receptor antagonists alone or in combination with corticosteroids were administered before each cisplatin dosing, and the doses were then tapered during the days thereafter.

Thromboembolic Events in Cases and Controls

Treatment-related thromboembolic events ("events") were defined as venous or arterial thrombosis or embolism occurring during the period between the first day of chemotherapy and 6 weeks (42 days) after the last administration of cytostatic drugs that belonged to the first-line chemotherapy regimen. Superficial thrombophlebitis, often related to the use of indwelling peripheral venous catheters, occurred frequently but was not included in the analysis. Deep venous thrombosis (DVT) presenting before the initiation of chemotherapy (n = 2), DVT occurring more than 6 months after the cessation of first-line chemotherapy (n = 3) or during second-line chemotherapy for a relapse of the disease 1 year later (n = 1), and vena cava syndrome without evidence of thrombosis in the caval or iliac vein (n = 4) were also not included in the analysis. Patients who developed one or more thromboembolic events were recorded as cases; all other patients were recorded as controls. Eight of the controls, including two patients with DVT or caval or iliac vein thrombosis before the start of chemotherapy and six other patients with a cardiovascular history, had already received coumarin before the start of chemotherapy.

Table 1. Risk Factors Analyzed

- Age
- Body weight and length
- (Family) History of vascular disease
- Smoking habits
- Lung function parameters, ie, vital capacity and hemoglobin-corrected diffusion capacity of lung for carbon monoxide
- Previous and concomitant surgical treatment or radiotherapy
- Histologic classification of primary tumor
- Side of primary testicular tumor (right or left)
- Extent of disease (sites of metastases)
- Prechemotherapy plasma tumor markers (erythrocyte sedimentation rate, lactate dehydrogenase, alpha-fetoprotein, beta-human chorionic gonadotropin)
- Prechemotherapy hematocrit
- Administration and doses of:
  - Cytostatic agents
  - Corticosteroids as part of antiemetic regimens
  - Serotonin-receptor antagonists as antiemetic therapy
  - Hematopoietic growth factors (granulocyte colony-stimulating factor)
  - Anticoagulant drugs (nonsteroidal anti-inflammatory drugs, coumarin, or heparin)
- Use of permanent intravascular access devices
- Use of intravenous contrast agents
- Prolonged immobilization during chemotherapy

Risk Factors

Risk factors for developing thromboembolic events, as mentioned in the literature,[28-33,36] were recorded (Table 1). Family history was considered to be positive if two or more first- or second-degree family members had a history of vascular disease. Patients who smoked one or more cigarettes per day in the 12-month period before the initiation of chemotherapy were defined as smokers. The results of pretreatment pulmonary function tests, available from patients treated with bleomycin, were only included in the analysis if the tests had been performed before the first administration of bleomycin.

The histologic classification of the major component of the primary tumor according to the World Health Organization was used for the diagnosis of the tumor,[37] combining embryonal carcinoma and tumors containing both embryonal carcinoma and teratoma into one group hereafter referred to as embryonal carcinoma. Other risk factors that were analyzed included IV contrast agents,[38] immobilization, and surgery. IV contrast agents administered for radiologic investigations in the 7 days preceding the thromboembolic event were scored; immobilization and surgery were scored if present within a 30-day period before the occurrence of thromboembolic events. The time period during which the complete first-line treatment was administered, including surgery after first-line chemotherapy (often retroperitoneal lymph node dissection for residual tumor masses) and consolidation chemotherapy, was included in our analysis.

Furthermore, for the cases, the creatinine clearance and serum magnesium concentration, parameters of cisplatin-induced renal toxicity (renal glomerular and tubular dysfunction, respectively) were recorded at the time of the first thromboembolic event, reflecting chemotherapy- and, in particular, cisplatin-induced toxicity. In addition, DNA isolated from WBCs of the 12 cases who are still alive was analyzed for gene mutations in factor V Leiden and prothrombin (factor II; 20210, G-to-A replacement), as previously described.[34,35]

Table 2. Characteristics of the Individual Cases and Thromboembolic Events in Relation to (Chemo)Therapy

Case No.	Start of CT	Age (years)	Type of Thromboembolic Event	Interval (days) Between Thromboembolic Event and: Start of CT	Last Administration of Cisplatin	Last Administration of Bleomycin	Surgery	Tumor Type	Site of Metastases	Regimen
1	1981	29	PE	102	35	24	17	embr ca	abd ln	PVB
2	1981	28	PE	87	13	14	104	chorio ca	abd ln, med ln, pulm	DOX-BEP
3	1982	28	PE	4	0	3	11	embr ca	abd ln, cerv ln, pancreas	PVB
	1982		PE	96	29	18	10		abd ln, cerv ln, pancreas	
4	1983	25	DVT	10	6	3	13	embr ca	abd ln, pulm, cerv ln, liver	PVB
5	1984	37	VT portal, splenic, and superior mesenteric vv	106	33	22	—	seminoma	abd ln, pulm, liver, CNS	PVB
6	1986	20	DVT	10	6	2	22	seminoma	abd ln, med ln	BEP
7	1987	37	PE	54	7	3	87	embr ca	Only elevated serum tumor markers	BEP
	1987		PE	79	11	1	112		Only elevated serum tumor markers	
8	1991	54	PE	39	7	2	63	seminoma	abd ln	BEP
	1991		AT iliac, femoral, and popliteal aa	49	1	4	73		abd ln	
9	1994	25	VT hepatic v	70	3	5	75	embr ca	abd ln, med ln, pulm, liver.pleura	BEP
10	1994	24	Cerebral ischemic stroke	52	6	3	230	embr ca	abd ln	BEP
11	1994	17	PE	59	12	12	51	embr ca	abd ln	BEP
12	1995	46	PE	37	12	2	218	embr ca	No measurable disease	BEP
13	1995	32	PE	52	5	1	155	embr ca	abd ln	BEP
14	1996	29	PE	63	16	4	95	embr ca	abd ln, pulm	BEP
15	1997	34	Cerebral ischemic stroke	9	5	2	60	embr ca	abd ln	BEP

Abbreviations: CT, chemotherapy; Surgery, lymph node dissection or orchidectomy; PE, pulmonary embolism; (D)VT, (deep) venous thrombosis; AT, arterial thrombosis; v, vein; vv, veins; a, artery; aa, arteries; embr ca, embryonal carcinoma; chorio ca, choriocarcinoma; abd ln, abdominal lymph nodes; med ln, mediastinal lymph nodes; pulm, pulmonary; cerv ln, cervical lymph nodes; PVB, cisplatin-vinblastine-bleomycin; DOX, doxorubicin; BEP, cisplatin-etoposide-bleomycin.

Statistical Analysis

We compared patients who experienced one or more thromboembolic events during their chemotherapy course (cases) with patients who did not experience such events (controls). The number of chemotherapy cycles did not differ significantly between cases and controls. Because all controls were observed for beyond the latest occurring events, we decided to analyze these data as a case-control study. First, we compared the baseline and treatment-related characteristics between cases and controls using the χ^2, Student's *t*-, or Mann-Whitney tests, as appropriate. To investigate possible risk factors, we calculated odds ratios as an estimate of the relative risk. The odds ratios show how much higher the risk of disease, eg, thrombosis, is in the presence of a risk factor than in its absence; an odds ratio of 1 indicates the absence of an association. Second, we used multivariable logistic regression analysis to estimate the contributions of several factors to the risk of thromboembolic events. Included in this multivariable model were all variables that had either a P value of .05 or lower in univariate analysis or an univariate odds ratio of 2.0 or higher.

RESULTS

Thromboembolic Events and Cases

Analysis of the first-line chemotherapy treatment period of the 179 patients treated in our hospital revealed a total of 18 major thromboembolic events. Fifteen (8.4%) of the 179 patients developed major thromboembolic events; 12 patients developed one and three patients developed two thromboembolic events during chemotherapy (Table 2). Three of the 18 events were caused by arterial thrombosis, namely, one patient (Table 2, patient no. 8) with thrombosis of both abdominal and leg arteries and two patients (Table 2, patients no. 10 and 15) with cerebrovascular accidents. In total, 15 venous thromboembolic events occurred in 13 patients (Table 2); these 13 cases developed DVT of the lower extremities (n = 2), abdominal venous thrombosis (n = 2), or pulmonary embolism (n = 11) and were treated with heparin and oral anticoagulant drugs. In the nine patients with pulmonary embolisms, the diagnosis was made with perfusion or ventilation-perfusion scans.

The thromboembolic events occurred between 4 and 106 days after the start of chemotherapy (mean interval for the first event, 50 ± 33 days; median, 52 days). Only two events occurred within 1 day after the administration of cisplatin (median, 7 days after cisplatin administration), and two other events occurred within 1 day after bleomycin administration (median, 3 days after bleomycin administration).

Fourteen cases underwent prior orchidectomy; in one case (patient no. 5), the intra-abdominally located pathologic testis was removed after chemotherapy. In contrast to

the more recently occurring thromboembolic events, five of the events occurring in the period between 1981 and 1987 occurred within 10 to 22 days after surgery (Table 2). In all five cases with abdominal or lower-extremity thromboembolic events, extensive abdominal metastases were found before the start of chemotherapy. In these five cases, three thromboembolic events occurred during the third and fourth chemotherapy cycle, after marked tumor regression had already occurred.

Of the 18 thromboembolic events that occurred, one (5.6%) was fatal; this case (patient no. 15) died as a consequence of the cerebrovascular event. In the control group, three (1.8%) of the 164 patients died, two because of respiratory failure after bleomycin-induced pulmonary fibrosis and one because of heart failure more than 45 days after the cessation of chemotherapy. Thus four (2.2%) of the 179 patients died as a result of complications during therapy. None of the cases had received IV contrast agents nor been immobilized in the 7 days preceding the thromboembolic event. Cases did not develop other excessive chemotherapy-related toxicity, as evidenced by the fact that the mean creatinine clearance at the time of the first thromboembolic event was 111 ± 32 mL/min (range, 61 to 164 mL/min) and the mean serum magnesium concentration was 0.73 ± 0.06 mmol/L (range, 0.64 to 0.85 mmol/L). Furthermore, no gene mutations of factor V Leiden or prothrombin were found in more recently analyzed leukocyte DNA of 12 cases who were still alive, making it unlikely that these two common risk factors for venous thrombosis contributed to these events.

Patients' Baseline Characteristics and Administered Chemotherapy

The baseline characteristics of cases and controls are listed in Table 3. Cases and controls did not differ with respect to age, body weight, and patient or family history of vascular disease, nor with respect to hematocrit value or lung function as measured by vital capacity and carbon monoxide diffusion capacity (age and patient's history of vascular disease only are listed in Table 3). Also the erythrocyte sedimentation rate and the median levels of lactate dehydrogenase and the serum tumor markers alpha-fetoprotein and beta-human chorionic gonadotropin before the start of chemotherapy did not differ between cases and controls. The percentage of patients who smoked and patients who underwent a retroperitoneal lymph node dissection was higher in the control group, compared with the cases (not statistically significant; Table 3). Cases and controls did not differ with respect to the side on which the primary testicular tumor had occurred (Table 3).

Eleven (73.3%) of the 15 cases had embryonal carcinoma, and three cases (20.0%) had seminoma. In contrast, 80 (48.8%) of the controls had embryonal carcinoma and 71 (43.4%) had seminoma. Patients with liver metastases had an increased risk for developing thromboembolic events (odds ratio, 4.9; 95% confidence interval, 1.1 to 20.8). Interestingly, patients who only had elevated tumor markers and who did not have measurable disease had a slightly increased risk for development of thromboembolic events (odds ratio, 4.9; 95% confidence interval, 0.9 to 27.7).

All cases had been treated with both cisplatin and bleomycin, in contrast to the controls, who, in some cases, received carboplatin instead of cisplatin and who were not always treated with bleomycin (data not shown). However, except for carboplatin, the mean total administered dose of cytostatic drugs was not different between cases and controls (Table 3). The controls even received a much higher mean cumulative dose of individual cytostatic drugs during the total treatment period (4.9 ± 2.1 cycles) than the mean cumulative dose of cytostatic drugs received in the period until the occurrence of the first thromboembolic event by the cases (2.7 ± 1.3 cycles). The total dose of administered cytostatic agents until the first thromboembolic event was 521 ± 202 mg, 200 ± 103 mg, 1,639 ± 793 mg, and 56 ± 18 mg for cisplatin, bleomycin, etoposide, and vinblastine, respectively.

Concomitant Surgery and Supportive Care–Related Risk Factors

About half of the cases and controls received dexamethasone as antiemetic therapy, whereas a higher percentage of cases than controls received serotonin receptor antagonists as antiemetic therapy (Table 4). Cases received a significantly higher mean dose of dexamethasone per cycle until the first thromboembolic event, compared with the mean dose of dexamethasone per cycle administered to controls during the entire treatment period (Table 4; Student's t test $P = .004$). High doses of corticosteroids, namely 80 mg or more of dexamethasone per cycle, were identified as a risk factor for the occurrence of thromboembolic complications (Table 4; odds ratio, 3.5; 95% confidence interval, 1.2 to 10.3).

None of the cases received hematopoietic growth factors or permanent intravascular access devices before the occurrence of the thromboembolic event. One of the cases and eight of the controls received nonsteroidal anti-inflammatory drugs, and eight of the controls received coumarin as an anticoagulant before the start of chemotherapy and during chemotherapy (see Patients and Methods).

Multivariable Logistic Regression Analysis

Multivariable logistic regression analysis identified both liver metastases and high doses of corticosteroids (≥ 80 mg

Table 3. Baseline and Chemotherapy Characteristics of Cases and Controls

	Cases (N = 15)		Controls (N = 164)		
	%	No	%	No.	P*
Age, years, mean ± SD	31.0 ± 9.6		30.7 ± 9.9		.91
History of vascular disease	13.3	2	11.0	18	.68
Smoking habits	26.7	4	45.1	74	.19
Prior orchidectomy	86.7	13	97.0	159	.11
Prior lymph node dissection	6.7	1	12.2	20	.99
Prior radiotherapy	0.0	0	11.6	19	.37
Laboratory parameter, median					
ESR, mm/1 h	19		16		.72
LDH, U/L	258		239		.87
α-FP, μg/L	22		7		.31
β-HCG, U/L	25		8		.85
Tumor histology					
Seminoma	20.0	3	43.3	71	.10
Embryonal carcinoma	73.3	11	48.8	80	.10
Choriocarcinoma	6.7	1	6.7	11	.99
Yolk sac tumor	0.0	0	1.2	2	.99
Right-sided primary testicular tumor	46.7	7	53.0	87	.79
Extragonadal tumor	13.3	2	6.7	11	.30
Site of metastases					
Elevated tumor markers only	13.3	2	3.0	5	.11
Abdominal lymph nodes	86.7	13	78.0	128	.74
Mediastinal lymph nodes	20.0	3	10.4	17	.38
Lungs	33.3	5	37.8	62	.79
Liver	20.0	3	4.9	8	.02
Visceral organs, excluding liver	20.0	3	14.0	23	.46
No. of chemotherapy cycles, mean ± SD	4.3 ± 1.7		4.9 ± 2.1		.27
Total dose of administered cytostatic agents, mg, mean ± SD†					
Cisplatin	815 ± 279		909 ± 327		.29
Carboplatin	0 ± 0		2065 ± 1125		.001
Bleomycin	278 ± 98		293 ± 99		.58
Etoposide	2556 ± 1141		2375 ± 995		.79
Vinblastine	56 ± 18		105 ± 93		.18

Abbreviations: ESR, erythrocyte sedimentation rate; LDH, serum levels of lactate dehydrogenase; α-FP, serum levels of alpha-fetoprotein; β-HCG, serum levels of beta-human chorionic gonadotropin.

*Significance of *t* test (*P*) for metric parameters.

†Patients who did not receive the drug were excluded.

dexamethasone per cycle), but not embryonal carcinoma or the presence only of elevated tumor markers, as independent risk factors for the development of thromboembolic complications during treatment (Table 5).

Review of the Literature

We reviewed the literature with respect to thromboembolic events occurring in germ cell cancer patients. Only thromboembolic events occurring in the time period after the start of chemotherapy until 42 days after the completion of chemotherapy were included in this review. Raynaud's phenomenon, unproven thromboembolic events such as "chest pain" without ECG changes, congestive heart failure, and "minor" events such as superficial thrombophlebitis were not taken into account. However, in contrast to our own 15 cases reported (Table 2), we did include in this review a few patients who developed thromboembolic complications during second-line chemotherapy. We thus identified 28 reports dealing with this subject. In these 28 reports, 48 germ cell cancer cases who developed a total of 56 proven major thromboembolic events were described (Table 6).[1-28]

Of the 56 thromboembolic events reported in the literature, 35 events (61.4%) occurred as a result of arterial disease; namely, 18 myocardial infarctions, 10 cerebrovascular events, and seven peripheral arterial occlusions. In our patients, only three (17%) of the 18 events were of arterial origin. The other 21 events reported in the literature consisted of 15 cases of DVT of the extremities or abdomen and six pulmonary embolisms.

Table 4. Concomitant Surgery and Supportive Care–Related Risk Factors of Cases and Controls

Treatment	Cases (n = 15)				Controls (n = 164)		OR*†	95% CI*†	P for t Test‡§
	Until First Thromboembolic Event		During Whole Treatment						
	%	No.	%	No.	%	No.			
Concomitant surgery during chemotherapy	26.6	4	40.0	6	34.8	57	0.68	0.21-2.24	
Dexamethasone	53.3	8	66.7	10	51.2	84	1.09	0.38-3.14	
Dose of dexamethasone/cycle									
≥ 20 mg dexamethasone/cycle	53.3	8	66.7	10	43.3	71	1.48	0.51-4.28	
≥ 40 mg dexamethasone/cycle	53.3	8	60	9	35.4	58	2.09	0.72-6.05	
≥ 60 mg dexamethasone/cycle	46.7	7	46.7	7	26.2	43	2.46	0.84-7.20	
≥ 80 mg dexamethasone/cycle	46.7	7	46.7	7	20.1	33	3.47	1.18-10.27	
Total dexamethasone dose, mg (mean ± SD)‖	—		349 ± 149		281 ± 161				.593
Dexamethasone dose/cycle, mg (mean ± SD)‖	93 ± 21		79 ± 26		62 ± 33				.127
Serotonin-receptor antagonists	46.7	7	46.7	7	32.3	53	1.83	0.63-5.32	

*Odds ratio and 95% confidence interval for nominal parameters.
†Comparing values of cases before thromboembolic event and of controls during the entire treatment.
‡Significance of *t* test (*P*) for metric parameters.
§Comparing doses administered to cases and controls during the entire treatment.
‖Patients who did not receive the drug were excluded.

Patients' ages, primary tumor histologies, and sites of metastases were not always reported in the literature. At least 11 (34.4%) of the 32 cases for whom age was reported were more than 40 years of age, and in 10 of the 11 cases the thromboembolic events reported were of arterial origin. In our series, only two (13%) of the 15 cases were more than 40 years of age. Eleven of the 53 thromboembolic events reported in the literature were fatal; of these 11 fatal events, six concerned venous thromboembolic events and the other five were arterial thromboembolic events. In seven studies dealing with various chemotherapy-related toxicities in large groups of germ cell cancer patients, the incidences of cardiovascular complications varied between 0.6% and 15.3%.[20-25,27]

DISCUSSION

In this study, a high incidence of major thromboembolic events was found in 15 (8.4%) of the 179 germ cell cancer patients undergoing chemotherapy in our department. Seventeen percent of the events were arterial, and one of the 18 events that occurred was fatal. Three cases developed two major thromboembolic events: two developed two venous events, whereas one developed a venous and an arterial event. Liver metastases and the administration of high doses of dexamethasone as antiemetic therapy were identified as risk factors for the development of thromboembolic complications. Interestingly, cases did not have excessive (other) chemotherapy-related toxicity at the time that the thromboembolic event occurred. No gene mutations of factor V Leiden or prothrombin were found in the cases. In the early 1980s, there seemed to be a temporal association between the occurrence of thromboembolic events and recent surgical treatment, whereas thromboembolic events that occurred since 1991 were often related to the use of high doses of the corticosteroid dexamethasone as an antiemetic.

Table 5. Multivariable Logistic Regression Analysis

	Odds Ratio	95% Confidence Interval
Embryonal carcinoma	2.43	0.69-8.55
Elevated tumor markers only	4.02	0.61-26.70
Mediastinal lymph nodes	1.57	0.32-7.60
Liver metastases	7.37	1.40-38.74
≥ 80 mg dexamethasone/cycle	3.34	1.00-11.30

In addition to the 15 patients who had thromboembolic events during chemotherapy, six additional patients had DVT before the start of chemotherapy, more than 6 months after the cessation of chemotherapy, or during second-line chemotherapy, resulting in an even higher incidence of 11.7% of the 179 included germ cell cancer patients treated in our hospital in the time period studied. Bredael et al[39] also found a high incidence of pulmonary embolism as the cause of death in 14 (9%) of the 144 autopsied germ cell tumor patients, suggesting that humoral factors of the tumor affect the hemostatic system. Most germ cell cancer cases reported in the literature who developed thromboembolic complications had embryonal carcinoma. In accordance with Stockler et al,[40] thromboembolic events occurred more often in patients with this histologic tumor type, ie, embryonal cell carcinoma or embryonal cell carcinoma plus teratoma, than in patients with seminoma. The findings that

Table 6. Thromboembolic Events During Chemotherapy in Germ Cell Cancer Patients: A Review of the Literature

First Author (ref)	Age (years)	Type of Tumor	Site of Metastases	Chemotherapy Regimen	Event	Fatal Event	Remarks*
Margileth[1]	30	"teratocarcinoma"	abd ln, med ln, cerv ln	Mithramycin	thr posterior tibial a and aa of the right hand	–	Mithramycin
Berman[2]	30	embr ca	abd ln	PVB	Seizure + cortical blindness	–	Platinum in CSF
Bodensteiner[3]	31	embr ca	abd ln	PVB	MI	–	Bleomycin
Cohen[4]	36	embr ca	abd ln-res	PVB	Hemianopsy + encephalopathy	–	Platinum in CSF
Bosl[20]	51	NR	NR	VAB-6	MI	–	1/166 patients
Doll[21]	25	embr ca	abd ln-res	PVB	CVA	–	2/23 patients
	27	embr ca	abd ln, liver	EP	MI	–	
Lederman[5]	26	choriocarcinoma	NR	EP-DOX	PE	–	Endothelial damage
	30	yolk sac tumor and choriocarcinoma	pulm	PVB	PE and pulmonary infarction	+	Endothelial damage
	31	embr ca	elevated tumor markers only	BEP	PE	–	Endothelial damage
Samuels[6]	23	"endodermal sack tumor"	med ln	PVB	Rectal infarction	+	Von Willebrand factor
	58	choriocarcinoma and embr ca	cerv ln, pulm	PVB	CVA	–	Von Willebrand factor
				CYC-ACTD-MTX	CVA	+	
	33	embr ca	abd ln, cerv ln, pulm, liver	Cytarabine	MI	+	Von Willebrand factor
Cantwell[22]	NR	NR	abd ln, pulm	EP-IFX	PE	+	Retroperitoneal lymph nodes larger than 5 cm in diameter, 9/52 patients, predominantly treated with PVB or BEP
	NR	NR	abd ln		Pulmonary infarction	–	
	NR	NR	abd ln	DVT	–		
	NR	NR	abd ln	DVT	–		
	NR	NR	abd ln	DVT	–		
	NR	NR	abd ln	DVT	–		
	NR	NR	abd ln, pulm, liver	DVT	–		
	NR	NR	pulm	CVA	–		
	NR	NR	abd ln, liver	MI	–		
Hall[7]	18	"malignant teratoma"	abd ln	PVB	PE and pelvic venous thrombosis	+	Retroperitoneal lymph nodes, pretreatment malignant caval thrombus
Stefenelli[23]	NR	NR	NR	PVB	Myocardial ischemia	–	Chest pain in 8/21 patients; only 1 documented with ECG changes
Clemm[24]	NR	seminoma	"stage IIC-IV"	VIP	MI	–	Previous coronary heart disease, 1/24 patients
Zeymer[8]	47	embr ca	abd ln-res	PVB	MI	–	Vinblastine
				PV	MI		
Berliner[9]	52	embr ca	NR	Cisplatin (after two courses of PVB)	MI	–	Cardiovascular risk factors in history
	57	seminoma	NR	BEP	MI	–	
Garstin[10]	35	"malignant teratoma"	med ln, pulm	BEP	thr femoral a	–	Pretreatment arterial disease
				BEP	thr popliteal a	–	
Borek[11]	21	"teratoma"	abd ln	EP-IFX	MI	+	During sepsis/ARDS
Gerl[12]	26	"malignant teratoma intermediate"	abd ln, pulm	BEP + prednisolone	CVA	+	Corticosteroids

Table 6. Cont'd

First Author (ref)	Age (years)	Type of Tumor	Site of Metastases	Chemotherapy Regimen	Event	Fatal Event	Remarks*
Nichols[25]	46	NR	NR	BEP	MI	–	4/159 patients
	NR	NR	NR	BEP	DVT	–	
	NR	NR	NR	BEP	DVT	–	
	NR	NR	NR	BEP	DVT	–	
Schwarzer[13]	28	"non-seminoma"	abd ln	BEP	MI	–	Bleomycin ± etoposide
Coates[26]	57	seminoma	abd ln, med ln	BEP	thr caval, iliac, femoral and popliteal vv	+	Ondansetron
	48	"testicular carcinoma"	NR	POMBACE + dexamethasone	Status epilepticus, visual field loss	–	
Ellis[27]	32	embr ca	abd ln	BEP	MI		Smoking, history of intravenous drug abuse; 1/47 patients
Gerl[14]	42	embr ca	pulm	BEP	CVA	+	
Içli[15]	19	"malignant teratoma"	pulm	EP	MI	–	Hypomagnesiemia
				EP	MI	–	Hypomagnesiemia
				EP	CVA	–	Hypomagnesiemia
Airey[16]	32	"mixed teratoma and seminoma"	"stage II"	ACE	MI	–	Etoposide
Schmidt[17]	45	choriocarcinoma	abd ln, pulm, liver	BEP + GCSF	thr fem a	–	Granulocyte colony-stimulating factor
Lepidini[18]	40	choriocarcinoma	pulm	PVB + GCSF	thr fem a	–	β-HCG and/or estrogens
				PVB + GCSF	thr iliac v, aorta, renal a	–	
Shlebak[19]	32	"germ-cell tumor"	"stage IE"	BEP	DVT	–	
	37	seminoma	"stage II"	EP	DVT	–	
Hassan[28]		NR	NR	NR	DVT	+	31 patients with inferior vena cava obstruction; 2 developed DVT during chemotherapy; 1 of these 2 patients died of PE
		NR	NR	NR	DVT	–	

NOTE. Quoted text indicates citation from the article.

Abbreviations: NR, not reported in the article; embr ca, embryonal cell carcinoma; abd ln, abdominal lymph nodes; abd-res, residual abdominal disease after retroperitoneal lymph node dissection; med ln, mediastinum; pulm, lungs; cerv ln, cervical lymph nodes; thr, thrombosis; a, artery; MI, myocardial infarction; CVA, cerebral vascular accident; PE, pulmonary embolism; DVT, deep venous thrombosis; v, vene; PVB, cisplatin, vinblastine, and bleomycin; vab-6, cyclophosphamide, vinblastine, bleomycin, dactinomycin, and cisplatin; EP, etoposide and cisplatin; DOX, doxorubicin; BEP, bleomycin, etoposide, and cisplatin; ACTD, actionomycin D; MTX, methotrexate; IFX, ifosfamide; VIP, vinblastine, ifosfamide, and cisplatin; PV, cisplatin and vinblastine; POMBACE, cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, and etoposide; ACE, actinomycin D, cyclophosphamide, and etoposide; GCSF, granulocyte colony-stimulating factor; ARDS, adult respiratory distress syndrome; β-HCG, serum levels of beta-human chorionic gonadotropin.

*Possible pathogenetic factors were suggested by the authors. Numbers indicate the number of events/number of patients in study.

several human teratocarcinoma cell lines release plasma membrane vesicles with procoagulant activity underscores the theory that this tumor type may be associated with the development of thromboembolic events.[41]

Other factors could explain why liver metastases are a risk factor for thromboembolic events in germ cell cancer patients. Although our findings are based on a small number of patients with liver metastases—namely, three cases and eight controls—the association between liver metastases and thromboembolic events has also been found in various other malignancies,[42,43] possibly because of the impaired clearance of activated coagulation factors and the decreased synthesis of anticoagulants in the liver.[32,43] Massive abdominal metastases (retroperitoneal lymph nodes and liver metastases) as a mechanical cause of venous thrombosis of abdominal and femoral vessels[7,22,28] seems unlikely, as in most of our patients, their large tumor masses that were present before the start of chemotherapy had already regressed by the time of the thromboembolic event.

One important finding of our study is that the administration of high doses of corticosteroids (≥ 80 mg dexamethasone per cycle) is an independent risk factors for the

development of thromboembolic events in germ cell cancer patients undergoing chemotherapy. This is in agreement with several reports about the hypercoagulable state of patients with Cushing's syndrome[44] and the occurrence of thromboembolic events in patients receiving high doses of corticosteroids or adrenocorticotropic hormone for various nonmalignant indications.[45-47] Also, the concomitant administration of corticosteroids as antiemetic therapy during chemotherapy in patients with germ cell cancer[12] and ovarian carcinoma[48] was suspected as the direct cause of thromboembolic events. Liver metastases and the administration of high doses of corticosteroids led to a considerable increased risk of venous thrombosis (three- to eight-fold increased risk). However, the numbers of cases and controls were small, and the contribution of these two factors to the occurrence of thromboembolisms should be confirmed in an independent study.

Various mechanisms contribute to the hypercoagulability induced by corticosteroids. For instance, corticosteroids may inhibit blood fibrinolytic activity[49] and decrease platelet count and levels of the clotting factor VIII/von Willebrand factor complex.[50] In addition, corticosteroids are known to decrease cerebral blood flow by their direct vasoconstrictive effect on cerebral blood vessels, increase blood pressure, and decrease the clearance rate of activated clotting factors by reticuloendothelial blockade.[51,52] Interestingly, in several studies of thrombotic events occurring during chemotherapy for patients with breast carcinoma[53,54] and hematologic malignancies,[55] patients often received corticosteroids as part of their antitumor chemotherapy regimens.

Cardiovascular risk factors, such as smoking and preexisting arterial disease, are frequently mentioned as risk factors for the development of thromboembolic events in germ cell cancer patients.[9,10,24,27] The older ages and more frequently reported arterial thromboembolic complications in the patients reported in the literature seem to agree with this. The high number of arterial thromboembolic events reported in the literature may result from selection bias toward reporting arterial but not venous complications in case reports.

The findings of our study indicate that germ cell cancer patients who undergo chemotherapy are at considerable risk of developing major thromboembolic complications. The identification of high doses of corticosteroids, equivalent to or greater than 80 mg dexamethasone per cycle, used as antiemetic therapy in highly emetogenic cisplatin-based chemotherapy regimens, as a risk factor for the development of such thromboembolic events suggests that the use of high doses of corticosteroids as antiemetic therapy should be avoided. On the basis of our findings, the prophylactic administration of heparin may be considered in germ cell cancer patients with liver metastases and in patients requiring high doses of corticosteroids as antiemetic therapy during chemotherapy. However, further studies should investigate the need for such treatment as well as evaluate its benefits. For instance, prophylactic administration of low-molecular-weight heparin has been demonstrated to be cost-effective in various other clinical settings[56] and could be considered in this patient population. Finally, because germ cell cancer cells may produce factors that cause a hypercoagulable state, we will investigate prospectively whether prothrombotic abnormalities are indeed present in patients with this type of cancer at the time of surgery or during chemotherapy for metastatic disease.

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