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Prognostic Significance of Venous Thromboembolic Events in Disseminated Germ Cell Cancer Patients

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Abstract

Background: Disseminated germ cell cancers are at high risk of developing thromboembolic complications. We evaluated the prognostic value of venous thromboembolic events (VTE) in disseminated germ cell cancer.

Methods: Patients with germ cell cancer receiving upfront platinum-containing chemotherapy between 2004 and 2014 were pooled from the Spanish Germ Cell Cancer Group (SGCCG) registry and reviewed for the presence of VTE. Results were validated in an independent international group of patients. We used a penalized Cox proportional hazards model including VTE as a time-varying covariate to identify and validate prognostic factors. All statistical tests were two-sided.

Results: The SGCCG registry identified 416 patients from 14 referral institutions. With a median follow-up of 49 months, VTEs were observed in 9% of patients ($n = 38$). Events occurred at diagnosis, during chemotherapy, and after chemotherapy in 2.6%, 5.0%, and 1.4% of patients, respectively. VTE was associated with shorter progression-free survival (PFS; hazard ratio [HR] = 2.29, 95% confidence interval [CI] = 1.18 to 4.47, $P = .02$) and overall survival (OS; HR = 5.14, 95% CI = 2.22 to 11.88, $P < .001$). In multivariable analysis, the effect was consistent in the intermediate-risk group, both for PFS (HR = 9.52 95% CI = 2.48 to 36.58, $P < .001$) and OS (HR = 12.84, 95% CI = 2.01 to 82.02, $P = .007$). VTE at diagnosis is also an adverse prognostic variable for progression-free survival (HR = 4.64, 95% CI = 2.04 to 10.54, $P < .001$) and for overall survival (HR = 6.28, 95% CI = 1.68 to 17.10, $P = .01$). These results were validated in an independent international cohort that included 241 patients from four hospitals.

Conclusions: VTE is an independent adverse prognostic factor in disseminated germ cell cancers, in particular for the intermediate prognostic group of the International Germ Cell Cancer Collaborative Group classification. The

presence of VTE at diagnosis has also prognostic significance and should be further explored in future prognostic classifications.

Germ cell cancer is the leading cancer in men younger than 35 years. Most germ cell cancers are located in the testis, whereas 5% to 10% arise outside the testis, mainly in the retroperitoneum, mediastinum, and the pineal region. A small proportion of germ cell cancers arise in women (1).

Despite improvements in diagnosis and chemotherapy delivery, a proportion of young patients are still dying from the disease (1,2). The most important prognostic factors are included in the International Germ Cell Cancer Collaborative Group (IGCCCG) classification. The IGCCCG classifies metastatic germ cell cancers in three distinct groups: good, intermediate, and poor prognostic groups (3). However, the identification of additional prognostic factors might help to adequately guide clinical trials with more aggressive treatments.

Disseminated germ cell cancers are at high risk of developing thromboembolic complications (4), with an estimated incidence of 9% to 10% (5–7). Most complications are venous thrombosis. These events might be related to disease-specific characteristics, as well as being related to cancer treatment (5,7–12).

Thromboembolic events have been associated with an adverse prognosis in several common cancers (13–17), suggesting a biologically more aggressive disease. However, the effect of thromboembolic complications on survival in germ cell cancer has not been studied.

In this study, we aimed to assess the prognostic significance of thromboembolic events in disseminated germ cell cancers.

Methods

Patient Population

All patients with disseminated germ cell cancer prospectively included in the Spanish Germ Cell Cancer Group (SGCCG) registry between 2004 and 2014 and treated with platinum-containing chemotherapy (BEP or EP), including 14 high-volume institutions, were reviewed for the presence of venous thromboembolism (training set). Disseminated germ cell cancer was defined as patients with stage II or III or persistent positive tumor markers postorchietomy. Patients with stage IA/B who received adjuvant chemotherapy were excluded.

As a validation group, we pooled all consecutive patients with germ cell cancer treated with platinum-containing chemotherapy during the same period of time at the *Instituto Nacional de Cancerología* (INCAN) in Mexico and three independent Spanish hospitals not included in the SGCCG registry.

A centralized institutional review board (IRB) at Morales Meseguer University Hospital, the Spanish Drug and Medicinal Products Agency (AEMPS), and an institutional review board at the INCAN in Mexico approved the study and did not require that every patient provide informed consent.

Data Collection

Data were collected from the individual medical records for all patients. For patients included in the prospective SGCCG

registry, individual electronic medical records were also reviewed to identify thromboembolic events.

All prognostic variables at diagnosis, including the TNM staging classification and the IGCCCG classification, were studied (3). A modified male IGCCCG classification was used for women (18). Other variables of interest included the presence of venous thromboembolic events (VTEs) and the date, location, and treatment of VTEs, together with the presence and date of progression and/or death.

VTE was defined as any venous thrombotic or embolic complication developed in patients treated with chemotherapy. Time of thrombosis was defined as VTE at diagnosis if the thromboembolic complication was observed at the moment of the diagnosis of germ cell cancer before treatment; during chemotherapy: events occurring from the first date of chemotherapy until one month after the last firstline chemotherapy; and postchemotherapy: all events occurring thereafter.

Progression-free survival (PFS) was defined as the time from tumor diagnosis to objective tumor progression or death from any cause. For those who did not experience progression or death, the outcome was considered left-censored for the purposes of the analysis. Overall survival (OS) was defined as the time from diagnosis to death from any cause. For those who did not experience death, the outcome was considered left-censored for the purposes of the analysis.

Statistical Analysis

Statistics were performed using the statistical software R (version 3.1.2). Descriptive analysis included absolute and relative frequencies, means, and standard deviations. To identify the prognostic significance of the thromboembolic events, we used a penalized Cox proportional hazards model including VTE and chemotherapy stage (pre, during, or post) as time-varying covariates (19,20). The proportionality assumption of Cox models was examined by visualizing Schoenfeld residuals for each predictor and by performing tests of nonzero slope. Two-tailed P values were calculated, and the statistical significance level was set at a P value of less than .05. When appropriate, 95% confidence intervals were provided.

Results

Overall, the training group consisted of 416 patients from the SGCCG that were reviewed for the development of VTE. Patient characteristics are described in [Table 1](#) and [Supplementary Table 1](#) (available online). Most subjects were male and diagnosed with testicular tumors. Extragonadal primary tumors were present in 3.8% of tumors. The most frequent histology was nonseminoma or mixed tumors. Most patients had metastatic disease. Regarding the IGCCCG classification, most patients had good prognosis (71.6%), followed by intermediate (16.6%) and poor prognosis (11.8%).

Treatment characteristics are described in [Table 1](#). All patients were treated with upfront chemotherapy. The most frequently used chemotherapy schedule was BEP (87.7%), followed by EP (12.3%). With a median follow-up of 49 months (range =

Table 1. Patient characteristics

Patient characteristics	SGCCG registry	Validation group	P
Total No. of patients	416	242	
Age, median (range), y	32 (10–71)	27 (16–69)	<.001*
Localization, No. (%)			
Gonadal	400 (96.2)	234 (96.7)	.72†
Extragenital	16 (3.8)	8 (2.3)	
Histology, No. (%)			
Seminoma	122 (29.3)	60 (24.8)	.20†
Non Seminoma	223 (53.6)	130 (53.7)	
Mixed	71 (17.1)	52 (21.5)	
IGCCC, No. (%)			
Good Prognosis	298 (71.6)	147 (60.7)	.01†
Intermediate Prognosis	69 (16.6)	50 (20.7)	
Poor Prognosis	49 (11.8)	45 (18.6)	
Chemotherapy (CT), No. (%)			
BEP	365 (87.7)	203 (83.9)	.17†
EP	51 (12.3)	39 (16.1)	
No. of CT cycles, median (range)	3 (1–7)	4 (2–6)	<.001
RPLND, No. (%)			
Yes	82 (19.5)	84 (34.7)	<.001†
No	310 (74.5)	157 (64.9)	

*Two-sided Student's *t* test. BEP = bleomycin, etoposide and cisplatin; EP = etoposide and cisplatin; IGCCC = International Germ Cell Consensus Classification; RPLND = retroperitoneal lymph node dissection; SGCCG = Spanish Germ Cell Cancer Group.

†Two-sided Pearson's chi-square test.

Table 2. Patient venous thromboembolic events and outcomes

Treatment and evolution	SGCCG registry	Validation group	P*
VTE, No. (%)			
Yes	38 (9.1)	34 (14.1)	.05*
No	378 (90.9)	208 (85.9)	
VTE by time of occurrence, No. (%)			
At diagnosis	11 (2.6)	7 (2.9)	.20†
During CT	21 (5.0)	20 (8.3)	
Post-CT	6 (1.4)	7 (2.9)	
Follow-up, median (range), mo	49 (0.2–226)	46 (1.8–125)	.09‡

* Two-sided Pearson's chi-square test. CT = chemotherapy; SGCCG = Spanish Germ Cell Cancer Group; VTE = venous thromboembolic events.

† Two-sided Fisher's exact test.

‡ Two-sided Student's *t* test.

0.2–226), cancer progression was observed in 68 patients (16.4%) and 28 patients (6.7%) died.

Venous thromboembolic events are described in [Table 2](#) and [Supplementary Table 2](#) (available online). VTE was observed in 38 patients (9.1%). VTE was present at diagnosis in 11 patients (2.6%), during chemotherapy in 21 patients (5.0%), and postchemotherapy in six patients (1.4%). Deep-vein thrombosis was present in 3.4% of patients, and pulmonary embolism in 4.8%. It should be noted that in six patients both events were confirmed concurrently. All patients received initial treatment with low-molecular weight heparins (LMWH). Out of the 38 patients who developed a VTE, 13 patients had disease progression and seven patients died. One patient with an advanced poor prognostic

Table 3. Prognosis of venous thromboembolic events in the Spanish Germ Cell Cancer Group Registry according to the prognostic group (IGCCCG classification)

Prognosis of VTE in the SGCCG	Progression-free survival		Overall survival	
	HR (95% CI)	P*	HR (95% CI)	P*
All patients	2.29 (1.18 to 4.47)	.02	5.14 (2.22 to 11.88)	<.001
By IGCCCG				
Good	0.74 (0.04 to 14.03)	.85	5.29 (0.04 to 666.18)	.50
Intermediate	9.52 (2.48 to 36.58)	.001	12.84 (2.01 to 82.02)	.007
Poor	1.22 (0.47 to 3.15)	.68	1.62 (0.55 to 4.77)	.38

*Cox proportional hazard models were used to calculate *P* values. All test were two-sided. Cox regression analyses were used for survival analysis. CI = confidence interval; HR = hazard ratio; IGCCCG = International Germ Cell Consensus Classification group; SGCCG = Spanish Germ Cell Cancer Group; VTE = venous thromboembolic event.

Table 4. Prognosis of venous thromboembolic events in the intermediate risk group of the IGCCCG classification at diagnosis in the Spanish Germ Cell Cancer Group Registry

IGCCCG Intermediate-risk group	Progression-free survival		Overall survival	
	HR (95% CI)	P*	HR (95% CI)	P*
VTE	9.52 (2.48 to 36.58)	<.001	12.84 (2.01 to 82.02)	.007
Smoking history	4.62 (1.48 to 18.76)	<.001	3.44 (0.97 to 12.14)	.06
RPLND	5.26 (1.48 to 18.76)	.01	2.84 (0.56 to 14.31)	.21

*Cox proportional hazard models were used to calculate *P* values. All test were two-sided. SGCCG = Spanish Germ-Cell Cancer Group; CI = confidence interval; HR = hazard ratio; IGCCCG = International Germ Cell Consensus Classification group; RPLND = retroperitoneal lymph node dissection; VTE = venous thromboembolic event.

tumor died due to pulmonary embolism after the first chemotherapy cycle before tumor response evaluation. All other patients died because of disease progression.

The presence of a VTE was associated with an adverse prognosis, with shorter progression-free survival (PFS; hazard ratio [HR] = 2.29, 95% confidence interval [CI] = 1.18 to 4.47, *P* = .02) and overall survival (OS; HR = 5.14, 95% CI = 2.22 to 11.88, *P* < .001) as shown in [Table 3](#).

In order to control possible confounding factors, we used a penalized Cox proportional hazard model including VTE and chemotherapy (CT) stage (pre, during, or post) as time-varying covariates, and the IGCCCG classification, retroperitoneal lymph node dissection, and smoking history as fixed covariates. We found a differential prognostic significance of VTEs by the risk groups of the IGCCCG classification ([Table 3](#); [Supplementary Table 3](#), available online). We observed that the prognostic significance of VTEs was particularly statistically significant in the intermediate-risk group. It was associated with a statistically significant detrimental effect both for PFS (HR = 9.52, 95% CI = 2.48 to 36.58, *P* = .001) and for OS (HR = 12.84, 95% CI = 2.01 to 82.02, *P* = .007) ([Table 3](#)). VTEs in other risk groups were not associated with a difference in PFS or in OS ([Tables 3](#) and [4](#)).

Additionally to the time-varying analysis, we assessed the relationship between VTE at diagnosis and prognosis ([Table 5](#) and [Figure 1](#), A and B). We observed that VTEs at diagnosis were associated with a statistically significantly detrimental effect both for PFS (HR = 4.64, 95% CI = 2.04 to 10.54, *P* < .001) and for

OS (HR = 6.28, 95% CI = 1.68 to 17.10, $P = .01$) (Figure 1, A and B). When analyzed by the IGCCCG risk groups, as it was observed for the whole group of thrombosis, the effect was statistically significantly more evident in the intermediate-risk group. In this group, there was a detrimental effect both for PFS

(HR = 9.32, 95% CI = 2.56 to 34.01, $P < .001$) and for OS (HR = 12.08, 95% CI = 2.11 to 51.88, $P = .009$).

The validation group consisted of 241 consecutive patients treated at institutions that are independent from the SGCCG during the same period of time. Patient and treatment characteristics in the validation group are described in Table 1 and Supplementary Table 1 (available online). The validation group included more advanced tumors according to the IGCCCG classification ($P = .01$), and VTE was observed in 34 patients (14%). The most frequent VTE was DVT (7.9%), followed by catheter-related thrombosis (4.1%). With a median follow-up of 46 months, 60 (28%) patients had progressed and 23 (10%) had died, all due to progressive disease.

VTEs are confirmed as an adverse prognostic factor in this series, with a detrimental effect for PFS (HR = 2.65, 95% CI = 1.46 to 4.82, $P = .001$) and for OS (HR = 5.34, 95% CI = 2.29 to 12.51, $P < .001$).

The prognostic significance of VTEs at diagnosis is also confirmed both for PFS (HR = 3.65, 95% CI = 1.38 to 9.66, $P = .009$) and for OS (HR = 7.11, 95% CI = 2.21 to 22.82, $P < .001$) (Figure 1, C and D) in the validation group. These results were also confirmed in the intermediate-risk group of the IGCCCG classification in the validation group (Supplementary Table 4, available online).

Table 5. Prognosis of VTEs at diagnosis in the Spanish Germ Cell Cancer Group Registry according to the prognostic group (IGCCCG classification)

Prognosis of VTE according to the IGCCCG risk classification	Progression-free survival		Overall survival	
	HR (95% CI)	P*	HR (95% CI)	P*
All patients	4.64 (2.04 to 10.54)	<.001	6.28 (1.68 to 17.10)	.01
IGCCCG				
Good	2.86 (0.53 to 15.47)	.22	12.07 (0.08 to 135.76)	.23
Intermediate	9.32 (2.56 to 34.01)	<.001	12.08 (2.11 to 51.88)	.009
Poor	2.02 (0.53 to 7.75)	.30	2.35 (0.26 to 9.53)	.38

*Cox proportional hazard models were used to calculate P values. All test were two-sided. CI = confidence interval; HR = hazard ratio; IGCCCG = International Germ Cell Consensus Classification; VTE = venous thromboembolic event.

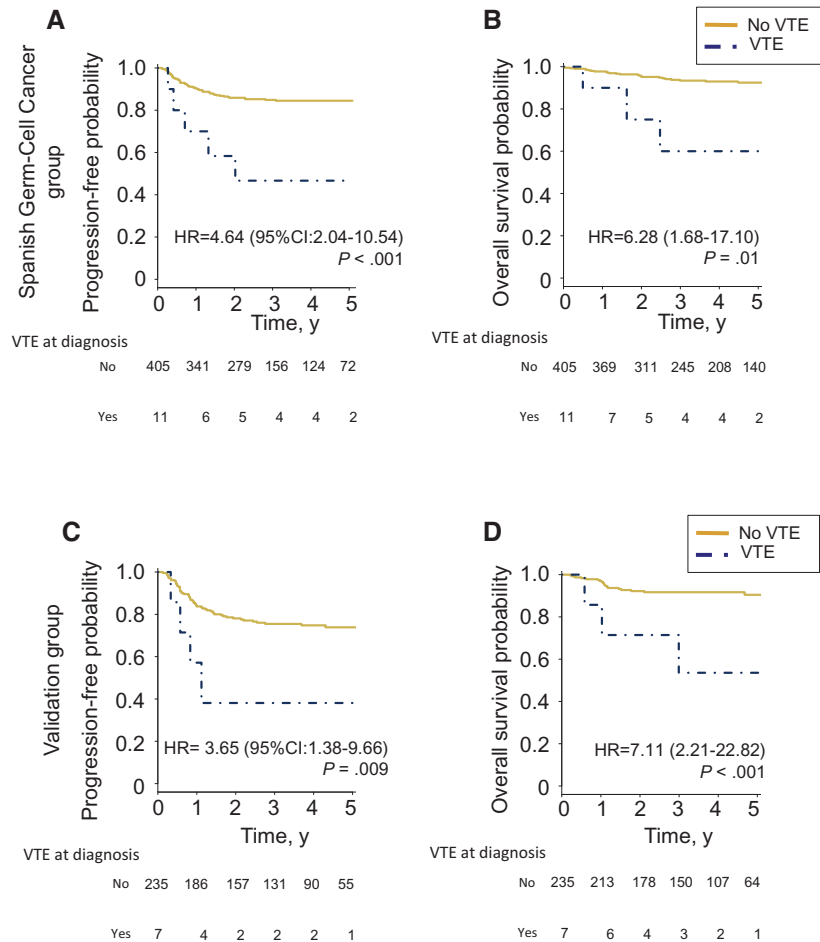


Figure 1 Kaplan-Meier survival curves by the presence of venous thromboembolic event at diagnosis. Progression-free survival and overall survival by venous thromboembolic events at diagnosis in the Spanish Germ Cell Cancer Group (SGCCG) (A and B) and in the validation group (C and D). Cox proportional hazard models were used to calculate P values. All tests were two-sided. CI = confidence interval; HR = hazard ratio; VTE = venous thromboembolic event.

Discussion

In this study, we report for the first time that the presence of VTEs in disseminated germ cell cancer is associated with an adverse prognosis. Strikingly this adverse prognostic feature is not directly associated with thromboembolic complications, but with disease progression and tumor-related death. In addition, we found that this adverse prognosis is particularly evident in the intermediate prognostic group, where it increases the risk of relapse more than nine times and the risk of death almost 12 times. The intermediate-risk group is sensitive to the inclusion of additional prognostic factors. While survival in the intermediate-risk group is good, the identification of a subset with the potential for a worse outcome is meaningful as it may be helpful for trial design or more aggressive therapies for this population.

This is the largest series of germ cell cancers reviewed for the development of VTE. The study was not restricted to those events that occurred during chemotherapy; it also included thromboembolic events that were already present at diagnosis, together with those that occurred after initial chemotherapy.

This finding was validated in an independent data set of patients treated according to international protocols. The patient characteristics in both series had several differences. The validation set was associated with more advanced disease and a higher proportion of patients in the intermediate and poor prognostic groups. As a consequence, it was also associated with a higher number of chemotherapy cycles, rate of retroperitoneal lymph node dissection, progression, and death. Interestingly, it was also associated with a higher rate of thrombosis. The validation group included hospitals not related to the SGCCG, and there might be unreported disparities in the patient population that could explain the differences because the test and validation sets were not drawn from the same population. The confirmation of the prognostic significance of VTEs in the validation group gives strength to the results.

The rate of thromboembolic events in this study (9%) is similar to the rates reported by other groups (5,7). Similar to previous reports, deep vein thrombosis was the most frequent VTE.

Interestingly, more than 25% of venous thrombotic events were already present at diagnosis. These events have been frequently excluded for analysis in other series that study the contribution of chemotherapy to the development of thrombosis. However, these events are of particular interest because they are purely induced by the tumor, either directly or indirectly, with no contribution of chemotherapy. The prognostic significance of these events can be useful because they are present at the moment that patients are being assigned to risk group categories and treatment plans are designed.

In this study, we observe that the presence of a VTE at diagnosis, in particular in the intermediate-risk group of the IGCCCG, is associated with an increase in the risk of tumor progression and death. Strikingly, all deaths in this group were related to tumor progression, and none to complications of thromboembolisms. This result might be related to a different biological aggressiveness of these tumors and needs to be further characterized.

More than 50% of VTEs occur during chemotherapy. These events might have mixed contributing factors, including tumor- and chemotherapy-related factors. Cisplatin-based chemotherapy is associated with the development of venous thrombosis in other cancer types, and it is also contributing to the development of VTEs in germ cell cancers (10–11,21). Cisplatin-based chemotherapy is associated with early vascular damage as well

as late cardiovascular toxicity (22,23). It might be clinically significant as one patient in the training group died because of a pulmonary embolism early after the first cycle of BEP. This event highlights the need to identify patients at high risk to develop thromboembolic complications and the opportunity to prevent VTEs in a population where chemotherapy achieves moderate-to-high cure rates. Prophylactic studies directed to prevent VTEs during chemotherapy in high-risk patients are needed.

Postchemotherapy VTEs also constitute a well-defined subgroup. The contributing factors to these events can also be complex, including residual vascular damage as a late effect of chemotherapy, as well as the presence of surgery for residual disease and tumor relapse and progression.

One limitation of the study is that the results come from a retrospective evaluation for the development of VTEs in patients prospectively included in the SGCCG registry. In order to reduce this limitation, patients were included starting in 2004, when most hospitals already had electronic records. In addition, the results were validated in a completely independent data set of patients, including patients from a different health care delivery system. Another limitation of the study is the low frequency of VTEs at diagnosis, which lowers the power of this variable and makes some confidence intervals particularly large.

The presence of VTE at diagnosis is associated with an adverse prognosis that is related to a higher risk of progression and tumor-related death. This might have implications for patient management because it is present before treatment decisions. The contribution of this factor to the current IGCCCG classification, in particular in the group with intermediate prognosis, should be better studied before making treatment variations. The contribution of VTE at diagnosis to the prognosis of patients at relapse should also be studied. It should also be highlighted that in this contemporary series of disseminated germ cell cancer treated with BEP/EP in the SGCCG, the survival of these patients is very good, with 93% of patients alive with a median follow-up of 49 months.

In conclusion, this is the first time that a study had identified the prognostic significance of VTE in disseminated germ cell cancer, in particular in the intermediate-risk group. We observed that VTE at diagnosis is a potential new prognostic factor in disseminated germ cell cancer. This might reflect a different biology, and it should be included in future studies adequately powered to improve the IGCCCG classification.

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