Stratification of Venous Thromboembolism Risk in Ovarian Cancer Patients During Chemotherapy

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Background: The prevalence of venous thromboembolism (VTE) in ovarian cancer during first-line chemotherapy (CHT) ranges between 6.4% and 10.6%. Identification of the susceptible population is crucial for effective thromboprophylaxis.

Methods: We performed a retrospective study of all our patients with epithelial ovarian cancer who underwent ambulatory first-line CHT between 1990 and 2004. Data were collected regarding age, body mass index (BMI), previous deep vein thrombosis, pulmonary embolism (PE), menopause status, FIGO stage, grade, histology, type of surgery, residual disease, and CHT. Univariable and multivariable regression analyses were performed to assess independent prognostic factors for VTE/PE to calculate a prognostic index (PI).

Results: Of 203 patients, 16 (7.8%) had symptomatic VTE: 15 deep vein thrombosis and 1 PE. Multivariable regression analysis found that age ($P = 0.01$), BMI ($P = 0.01$), and stage ($P = 0.05$) were independent prognostic factors for VTE. Age, BMI, and stage were used to calculate the PI: $0.285 \times \text{age} + 0.555 \times \text{BMI} + 1.110 \times \text{stage}$. The PI was dichotomized according to its median cutoff (5.8) to define a low (3.8% at 6 months) and a high (11.3%) VTE incidence group.

Conclusions: Age, BMI, and stage permit to identify ovarian cancer patients with a high risk in developing symptomatic VTE during CHT.

Key Words: Venous thromboembolism, Ovarian cancer, Chemotherapy, Prognostic index

(*Int J Gynecol Cancer* 2009;19: 79–83)

Patients with cancer have a 6-fold increased risk of venous thromboembolism (VTE) compared with those without cancer. Active cancer accounts for almost 20% of all new VTEs occurring in the community; furthermore, VTE is one of the most common complications seen in cancer patients.[1]

The etiology of thrombosis in malignancy is multifactorial, and mechanisms for thrombosis include release of procoagulant factors by tumor cells, stasis, and vascular injury.

It is generally accepted that the incidence of VTE in cancer patients is high. The exact risk in each patient depends on the tumor type, extent of cancer, and type of anticancer therapy,[2,3] but the presence of extrinsic risk factors such as older age, being bedridden, and comorbidities may also predispose to thrombotic complications in patients with cancer.[4,5]

Although deep vein thrombosis (DVT) is a serious complication and, in particular, pulmonary embolism (PE) is a quite frequent cause of death among patients with malignancies, there are few data that allow to predict which cancer patients, other than surgical patients,[6] would develop VTE.

Chemotherapy (CHT) is commonly recognized as and inducer of thrombosis with several factors such as endothelial cell damage or change and decrease in anticoagulant proteins.[7,8] However, patients with an advanced malignancy who are hospitalized with acute medical illness and are bedridden should received prophylaxis[6,9]; prevention of VTE is not routinely given to patients with cancer being ambulatory treated with CHT.

The identification of a quite high incidence of VTE in breast cancer patients receiving CHT has led to hypothesize the utility of thromboprophylaxis in this group,[10] but so far, still few data are provided in other cancer types and particularly in ovarian cancer patients.

In a previous study, we found that the incidence of symptomatic VTE throughout the entire history of ovarian malignancy is 16.6%, and the period with the highest probability to have the event is during first-line CHT (6.4%).[11]

We performed a retrospective study to identify the population with a higher risk to have VTE among ovarian cancer patients under first-line CHT.

MATERIALS AND METHODS

We reviewed the charts of patients with epithelial ovarian cancer whose conditions were consecutively diagnosed, treated, and followed up at the San Matteo Hospital in Pavia from 1990 to 2004.

We included patients with histologic diagnosis of epithelial ovarian cancer, treated with surgery and ambulatory CHT, followed up for at least 3 months after first-line CHT.

We excluded patients with inadequate information about surgery, histology or cytology, and VTE at diagnosis or after surgery.

All patients who underwent surgery received antithrombotic prophylaxis as follows: from year 1990 to 1999, unfractionated

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ISSN: 1048-891X
DOI: 10.1111/IGJ.0b013e318199035e

heparin (5000 IU 3 times a day); from year 2000 onward, low–molecular weight heparin (LMWH; 4000 IU every day), given for at least 7 days starting the evening before surgery or up to mobilization; and from 2002, LMWH (4000 IU every day) given for 28 days.

Data Collection

For each patient, data regarding age at diagnosis, body mass index (BMI), previous history of DVT or PE, menopause status, FIGO stage, grade, histology subtype, type of surgery, residual disease, and first-line CHT were collected.

The diagnosis of DVT and PE was objectively assessed after clinical suspicion of an event by compression ultrasound for lower limb DVT and spiral computed tomography for PE.

In particular, we considered 4 types of surgeries or procedures: 1) paracentesis for cytologic evaluation of ascites; 2) explorative laparotomy with biopsy; 3) monolateral or bilateral salpingo-oophorectomy with or without total hysterectomy, appendicectomy, and intraperitoneal and extraperitoneal biopsies; 4) monolateral or bilateral salpingo-oophorectomy with or without total hysterectomy, appendicectomy, intraperitoneal and extraperitoneal biopsies, omentectomy, pelvic para-aortic lymphadenectomy, and debulking procedures. The residual tumor after surgery was classified as absent, 2 cm in diameter or less, greater than 2 cm in diameter, and carcinosis.

The first-line CHT schedules were as follows: cysplatinum (CDDP 50 mg/mq weekly); cysplatinum + other drugs (CDDP 50 mg/mq + cyclophosphamide 600 mg/mq ± adriamycin 45 mg/mq every 3–4 weeks); carboplatin (JM8 AUC6 every 3–4 weeks); carboplatin + other drugs (JM8 AUC6 + paclitaxel 175–225 mg/mq every 3 weeks, JM8 AUC6 + epirubicin 120 mg/mq every 4 weeks, JM8 AUC5 + paclitaxel 175 mg/mq + topotecam 1 mg/mq per 3 days every 3 weeks).

End point and Design of the Study

This is an observational longitudinal retrospective study aiming at identifying independent predictors of VTE occurring during CHT and in the first month thereafter in a series of consecutive patients diagnosed with ovarian cancer at our center.

Statistical Analysis

Data were described as mean (SD) and as median and 25th to 75th percentiles if continuous and as counts and percentages if categorical.

We used the Kaplan-Meier method to calculate the cumulative VTE-free survival since the start of CHT. We calculated VTE rates per 100 person-year. Cox models were fitted to assess the prognostic role of a series of potential risk factors for VTE. The following variables were evaluated: age, BMI, residual tumor, previous DVT, menopausal state, FIGO stage (III/IV vs I/II), grading (3/4 vs 1/2), histologic diagnosis (clear cell vs other), and mono CHT (CDDP or JM8 vs combined). Those showing a $P < 0.10$ at the univariable analysis were included in a multivariable model (after checking for collinearity). The proportional hazard assumption of the models was verified by means of a test based on Schoenfeld residuals. Model validation was performed by computing the Maddala explained variation, the shrinkage coefficient for calibration, and the Harrell *C* statistics for discrimination. Discrimination was also assessed graphically by plotting the VTE-free survival curves corresponding to low- and high-risk groups. These were obtained by dichotomizing the prognostic index (PI = linear combination of the predictors in the model) according to its median value. The sensitivity and specificity, with the positive and negative predictive values (PPV and NPV), for identifying a VTE within 6 months with this classification were computed in those patients who had failed within 6 months or who had an observation time of at least 6 months. For the analysis of the VTE end point, patients dying were censored. 95% confidence intervals (95% CIs) were computed for the estimated parameters. Stata 9.2 (Stata Corporation) was used for computation. A 2-sided P value <0.05 was considered statistically significant.

TABLE 1. Patients characteristics

Variable	Description	Variable	Description
Age, mean (SD)	60.3 (11.54)	Grade, n (%)	
		1	10 (5.2)
		2	45 (23.3)
		3	129 (66.8)
		4	9 (4.7)
BMI, mean (SD)	24.7 (4.52)	Histologic diagnosis, n (%)	
		Clear cell	13 (6.7)
		Endometrioid	24 (12.3)
		Mucinous	19 (9.7)
		Serous	117 (60)
		Undifferentiated	9 (4.62)
		Others	13 (6.7)
Previous DVT/PE, n (%)	6 (3)	Type of surgery,* n (%)	
		0	7 (3.4)
		1	11(5.4)
		2	38 (18.7)
		3	147 (72.4)
Menopause status, n (%)	160 (78.8)	Residual tumor,† n (%)	
		No	62 (30.8)
		≤2	32 (15.9)
		>2	107 (53.2)
FIGO stage, n (%)		First-line CHT,‡ n (%)	
Ia	15 (7.4)	CDDP	55 (27.1)
Ib	1 (0.5)	CDDP + other	52 (25.6)
Ic	16 (7.9)	JM8	9 (4.3)
IIa	2 (1)	JM8 + other	85 (41.9)
IIb	4 (2)	Others	2 (1)
IIc	7 (3.5)		
IIIa	2 (1)		
IIIb	9 (4.5)		
IIIc	120 (59.4)		
IV	26 (12.9)		

*Surgery: 0, no surgery; 1, explorative bioptic laparotomy; 2, monolateral or bilateral salpingo-oophorectomy with or without total hysterectomy, appendicectomy, or intraperitoneal and extraperitoneal biopsies; 3, monolateral or bilateral salpingo-oophorectomy with or without total hysterectomy, appendicectomy, intraperitoneal and extra peritoneal biopsies, omentectomy, pelvic and para-aortic lymphadenectomy, or debulking.

†Residual tumor after surgery (cm).

‡Chemotherapy schedule: 0, no CHT; CDDP, cysplatinum; CDDP + other, cysplatinum + other (cyclophosphamide, adriamycin); JM8, carboplatin; JM8 + other, carboplatin + other (paclitaxel, epirubicin, topotecam).

RESULTS

Presenting Characteristics

A total of 224 patients with epithelial ovarian cancer were retrieved from the chart review. Twenty-one patients did not satisfy the inclusion/exclusion criteria, thus 203 patients, aged 60 (SD 12) years were enrolled into the study. Patient characteristics are summarized in Table 1. Only few patients had a history of DVT/PE. Most were in menopause. More than 75% were in FIGO stage III/IV, and most were graded 3 or 4. Sixty percent had a serous histologic diagnosis. Seventy percent of the patients had undergone monolateral or bilateral salpingo-oophorectomy with or without total hysterectomy, appendicectomy, intraperitoneal and extraperitoneal biopsies, omentectomy, pelvic and para-aortic lymphadenectomy, or debulking. Half of the patients had a residual tumor of more than 2 cm in size. Mono CHT had been used in one third of the patients. Chemotherapy had started after a median of 17.5 days (25th–75th, 13.0–22.0 days) after surgery, and patients had been observed to detect the occurrence of VTE for a median of 7.0 months (25th–75th, 6.2–7.0 months) since the start of CHT.

At the clinical or surgical evaluation after completion of first-line CHT, we observed 40 progressions (20%), 6 stable diseases (3%), 45 partial responses (22%), and 112 complete responses (55%).

Venous Thromboembolism During CHT

Sixteen patients had a VTE (of which 1 was PE) occurring during CHT, corresponding to an event rate of 15.6 per 100 person-year (95% CI, 9.6–25.5 per 100 person-year) or 1.3 per 100 person-month (95% CI, 0.8–2.1 per 100 person-month). Venous thromboembolism had occurred at a median of 2 months since the start of CHT (25th–75th, 1–3 months). In fact, all VTE occurred within 6 months since the start of CHT, and the cumulative VTE-free survival 6 months after the start of CHT was 91.6% (95% CI, 86.7%–94.8%). Nine patients had died during CHT and were censored at the time of their death. Table 2 reports the results of the univariable analysis. Age, BMI, mono CHT, and, marginally, FIGO stage were associated with an increased risk of VTE.

At the multivariable analysis including age, BMI, FIGO stage, histologic diagnosis, and mono CHT (Table 3), we identified the following independent predictors: BMI, histologic diagnosis, mono CHT, and, marginally, FIGO stage. The model performance was fair to good. On the basis of the Cox model, we were able to calculate a PI to categorize patients in lower and higher risk groups. In this series, the 94 patients included in the high-risk group had their likelihood of developing VTE almost 3 times higher ($P = 0.065$) than patients in the low-risk group.

The 6 months' incidences of VTE were computed to be 3.8% (95% CI, 1.4%–10.1%) and 11.3% (95% CI, 6.1%–21.0%) in the low- and high-risk groups, respectively.

Moreover, the sensitivity and specificity for observing a VTE within 6 months were 71% and 57%, with PPV and NPV of 14% and 95%, respectively, for an observed prevalence of events of 8.8% at 6 months. Given the current guidelines for first-line CHT for ovarian cancer, where mono CHT is not any more a criterion standard, we refitted the multivariable Cox model without including CHT. Results were not substantially different, although model performance decreased when removing this relevant predictor (Table 3).

DISCUSSION

Chemotherapy is an independent risk factor for VTE. In the Olmsted country population-based study, the risk of VTE was

TABLE 2. Evaluation of potential risk factors for DVT/PE occurring during CHT

	Level	No. Events	Rate per 100 Person-Year (95% CI)	HR (95% CI)	*P*
Age	(per 5-year increase)				
	≤61	5	9.3 (3.8–22.2)		
	>61	11	23.4 (13.0–42.4)	1.33 (1.03–1.71)	0.019
BMI	(per 5-point increase)				
	≤24.5	5	9.9 (4.1–23.7)		
	>24.5	11	20.5 (11.0–38.0)	1.67 (1.17–2.38)	0.017
Prior DVT	No	15	15.3 (9.2–25.3)		
	Yes	1	37.0 (5.2–263)	2.2 (0.3–16.9)	0.488
Menopause	No	2	8.3 (2.1–33.2)		
	Yes	14	18.2 (10.8–30.8)	2.1 (0.5–9.0)	0.298
FIGO stage	I-II	1	3.9 (0.6–28.8)		
	III-IV	15	20.0 (12.0–33.2)	4.8 (0.6–36.32)	0.055
Histologic diagnosis	Other	6	28.3 (12.7–63.0)		
	Clear cell/mucin	9	11.8 (6.2–22.7)	0.4 (0.1–1.2)	0.114
	Other	14	15.5 (9.1–26.1)		
	Clear cell	1	15.0 (2.1–106)	1.0 (0.1–7.3)	0.966
Grading	1/2	6	22.0 (5.9–49.0)		
	3/4	9	11.8 (6.2–22.7)	0.6 (0.2–1.7)	0.348
Residual tumor	No	3	8.8 (2.8–27.3)		
	Yes	13	19.8 (11.5–34.1)	2.1 (0.61–7.57)	0.196
CHT	Combined	6	8.4 (3.8–18.6)		
	Mono	10	34.2 (18.4–63.6)	4.07 (1.48–11.2)	0.007

TABLE 3. Multivariable Cox model for identifying patients with VTE during CHT

Variable	Level	Model With CHT, HR (95% CI)	*P*	Model Without CHT, HR (95% CI)	*P*
Age5*	Per 5-year increase	1.27 (0.94–1.70)	0.115	1.31 (0.96–1.78)	0.085
BMI5†	Per 5-year increase	1.62 (1.08–2.42)	0.019	1.49 (1.00–2.21)	0.047
FIGO stage	III-IV vs I-II	7.14 (0.81–62.89)	0.076	5.43 (0.64–446.4)	0.122
Histologic diagnosis	Clear cell/mucinous vs other	0.20 (0.05–0.78)	0.021	0.31 (0.09–1.05)	0.061
CHT	Mono vs combined	4.97 (1.50–16.49)	0.009	–	–
Model Validation	Estimates			Estimates	
P	0.001			0.010	
Explained variation	0.10			0.07	
Shrinkage coefficient	0.76			0.70	
Harrell *C*	0.78			0.73	
Prognostic index	PI = 0.047 × Age5 + 0.096 × BMI5 + 1.966 × Stage − 1.608 × Histology + 1.604 × mono CHT			PI = 0.054 × Age5 + 0.080 × BMI5 + 1.692 × Stage − 1.178 × Histology	
Risk category, HR (95% CI)	High >5.8 vs low ≤5.8	2.81 (0.88–8.96)	0.065	4.11 (1.14–14.7)	0.016
Sensitivity	71% (42%–92%)			79% (49%–95%)	
Specificity	57% (48%–65%)			57% (48%–65%)	
PPV	14% (7%–24%)			15% (8%–25%)	
NPV	95% (88%–99%)			96% (90%–99%)	

*Age5 = age/5.
†BMI5 = BMI/5.

increased 6.5-fold (95% CI, 2.1- to 20.2-fold) in patients with malignancy receiving CHT and 4.1-fold (95% CI, 1.9- to 8.5-fold) in patients with malignancy not receiving CHT compared with patients without malignancy.[1]

The relation between VTE and CHT has been most extensively investigated in patients with breast cancer. The incidence of VTE during CHT is as high as 7% in patients with stage II breast cancer[12] and approximately 17% in stage IV breast cancer,[13] and the addition of tamoxifen to CHT increases the thrombotic risk as compared with CHT alone.[14] Other advanced cancers are also likely to be associated with a high risk of thromboembolism during CHT.

In patients with high-grade glioma treated with CHT, the incidence of VTE was 12% in a prospective study[15] and 16% in a retrospective study.[16] Shapiro et al[17] reported an incidence of 17% in patients with unresectable or metastatic colon carcinoma treated with a combination of fluorouracil and leucovorin and granulocyte colony-stimulating factor.[18] The risk of VTE in patients receiving thalidomide has been found to range from 12% to 28% in combination with dexamethasone and/or other CHT.[19]

There are few data available on the incidence of VTE during CHT for ovarian cancer.

The present analysis indicates that among patients with ovarian cancer treated with CHT, the risk of symptomatic VTE is quite high with an incidence of 7.8% at 6 months. These data are in line with the incidence (10.6%) reported in another study that used screening impedance plathysmography to evaluate 60 ovarian cancer patients during CHT.[20] A recent study based on the California Cancer Registry reports a 2-year VTE cumulative incidence of 5.2 with an incidence rate of 19.3 events per 100 person-year comparable with the 15.6 per 100 person-year of our current study.[21]

In this study, independent predictors of VTE at the multivariable analysis were a larger BMI, histologic finding other than clear cell or mucinous, mono CHT with either CDDP or JM8, and, marginally, a FIGO stage III to IV. A larger BMI had already been related to VTE in a study of a small number ovarian cancer patients with DVT during CHT compared with patients without DVT.[20] The California Cancer Registry study showed that the stage of disease together with an older age and the presence of 2 or more chronic comorbidities of medical conditions are independent risk factors for VTE.[21]

A high incidence of DVT in invasive histology compared with borderline ovarian tumor was observed in the California Cancer Registry; other reports support a significantly increased incidence of VTE in patients with clear cell carcinoma when compared with other epithelial ovarian cancers.[21] In addition, our previous work about incidence of VTE in different histotypes of ovarian cancer suggests a higher risk of thromboembolic events in clear stage I carcinoma especially at diagnosis.[22,23] This could explain the low prevalence of VTE in patients with clear cell carcinoma during CHT.

We found that poly CHT has a statistically significant protective effect against VTE when compared with mono CHT. In 86% of our cases, the mono CHT was a weekly cysplatinum regimen (cysplatinum 50 mg/mq weekly). A recent report found an incidence of 16.7% of VTE in patients with cervical cancer treated with definitive chemoradiation and CCDP weekly concomitant

CHT,[24] suggesting the possibility of a higher thrombotic effect of this regimen.

Routine prophylaxis of ambulatory cancer patients with anticoagulation is not recommended with the exception of patients receiving thalidomide or lenalidomide, although in hospitalized cancer patients, antithromboprophylaxis should be considered.[19]

However, a problem of prophylaxis underuse to nonsurgical cancer patients exists. In a worldwide survey of perceptions and practices regarding VTE risk among 3891 oncologists, 52% would use prophylaxis routinely in cancer patients requiring surgery, but in fewer than 5% of cases in which surgery was not planned.[25] Reasons for the underuse of thromboprophylaxis in nonsurgical patients include the opinion that VTE risk is low, perhaps because this risk can vary by up to 10-fold according to diagnosis.[3]

On the basis of the fitted multivariable model (including also age), we stratified our patients in lower and higher risk groups. Patients in the high-risk group had a 3-fold higher risk of developing VTE. The sensitivity of this classification to predict VTE within 6 months from start of CHT was sufficiently high (71%), although the specificity was lower (57%). Moreover, the NPV was very high (95%), but the positive value was low (14%). Basing the classification of patients on another model not including the type of CHT (given the lack of current indication of mono CHT), we had similar results.

The main limit of this study is the low power related to a low incidence of VTE in this large series leading to a limited model performance and to a low PPV. In fact, our predictive algorithm showed a good sensitivity (high prevalence of patients with VTE in the high-risk group) and a moderate specificity; with this classification, we will be able to accurately identify patients who would not (high NPV), but not patients who would (low PPV), experience VTE during CHT. This last, however, is a common feature of rare events.

In conclusion, our study allowed to identify several risk factors for the occurrence of VTE during CHT and to classify patients in low- and high-risk groups. Although patients in the low-risk group might be left alone, patients in the high-risk group might use administration of a prophylactic anticoagulation. A low dose of warfarin and LMWH are effective in reducing the rate of thrombosis during CHT,[10,19] but there are still few data available on these results.

The 2004 American College of Chest Physicians guidelines recommended pharmacologic prophylaxis with either low-dose heparin or LMWH for bedridden patients with active cancer.

Prolonging the duration of surgical prophylaxis up to the end of CHT could be an option in these ambulatory high-risk patients.

This retrospective observational study should be confirmed, and the efficacy and safety of anticoagulant drugs in this setting should be tested.

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