Gynecologic Oncology 116 (2010) 374–377

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

When 'never-events' occur despite adherence to clinical guidelines: The case of venous thromboembolism in clear cell cancer of the ovary compared with other epithelial histologic subtypes ☆

Linda R. Duska [a,*], Leslie Garrett [b], Melissa Henretta [a], J. Stuart Ferriss [a], Lisa Lee [c], Neil Horowitz [d]

[a] Division of Gynecologic Oncology, University of Virginia Health Systems, PO Box 800712, Charlottesville, VA 22903, USA
[b] Division of Gynecologic Oncology, Massachusetts General Hospital, Boston, MA, USA
[c] Department of Obstetrics and Gynecology, Santa Clara Valley Medical Center, San Jose, CA, USA
[d] Division of Gynecologic Oncology, Brigham and Women's Hospital, Boston, MA, USA

ARTICLE INFO

Article history:
Received 3 August 2009

Keywords:
Ovarian cancer
Clear cell
Venous thromboembolism
Endometriosis

ABSTRACT

Objective. To determine the incidence of clinically significant venous thromboembolism (VTE) in women diagnosed with clear cell carcinoma of the ovary (CCC-O) interpreted in the context of Centers for Medicare and Medicaid Services (CMS) 'never-events.'

Methods. Using the institutional pathology Tumor Registry at the Massachusetts General Hospital (MGH), all women diagnosed with a CCC-O from 1994 to 2004 were identified. Controls with epithelial ovarian cancer of other histologies were matched for stage, age and year of diagnosis. Medical records were abstracted and pathology reviewed. All patients had surgical staging and/or cytoreductive surgery by a Gynecologic Oncologist at the MGH. All patients received appropriate peri- and post-operative prophylaxis with subcutaneous heparin and/or sequential compression devices. VTE was diagnosed with standard imaging techniques when clinical suspicion arose.

Results. Fifty-eight (58) women were diagnosed with CCC-O during the study period, 43 of whom had complete data available for analysis. Patients with Stage I or II disease comprised 70% of the patients. The mean age of the cohort was 55 and the mean weight 71 kg. Eighty-six (86) age, stage, and year of diagnosis matched controls were selected. The majority of controls had serous tumors (47%) with the remainder being endometrioid (33%), mucinous (14%), transitional cell (2%), sarcoma (2%) and mixed (2%). CCC-O was often seen in association with endometriosis 70% compared with 22% of controls ($p<0.0001$). Overall, 18 of 43 CCC-O patients (42%) had VTE while only 19 of 86 control patients (22%) had VTE ($p=0.024$, OR = 2.5 CI 1.1504–5.60). The rate of VTE was not influenced by weight or smoking. In the CCC-O patients, seventeen percent (17%) of VTE was diagnosed at presentation while 50% was diagnosed postoperatively and 33% at the time of disease recurrence or progression. Overall, including cases and controls, late stage disease was more likely associated with VTE (18 of 39, 46%) *vs.* early stage disease (19 of 90, 21%), $p=0.004$.

Conclusions. Women with CCC-O have a 2.5-times greater risk of disease related VTE than women with other histologies of epithelial ovarian cancer despite adherence to prophylactic guidelines. Given the high rate of VTE postoperatively as well as with disease recurrence, one should consider indefinite therapeutic anticoagulation in women with CCC-O. The case of CCC-O is one example of the impracticality of payment denial for 'never-events,' as VTE arises despite best efforts at prevention.

Introduction

Venous thromboembolism (VTE) has been identified as a significant healthcare quality issue and focus for the Centers for Medicare and Medicaid Services (CMS) [1]. Preventing VTE and its complications (such as pulmonary embolism) remain a national priority for healthcare quality. In fact, the use of preventative therapy for VTE is among the performance measures that hospitals are required to report to CMS in order to receive full Medicare payment for services. Importantly, CMS has identified the occurrence of VTE in the inpatient setting of knee and hip surgery as a targeted 'never-event' leading to payment denials [2]. If carried over to the DVT in the general hospital population in the future, this designation may lead to decreased Medicare payments to hospitals.

Gynecologic malignancies in general, and ovarian cancer in particular, have been associated with high rates of VTE, even in the setting of appropriate use of VTE prophylaxis [3]. Clear cell carcinoma of the ovary (CCC-O) is the ovarian histologic subtype that has been associated most frequently with an unusually high rate of VTE [4,5].

☆ This paper was presented in abstract form as a poster at the 38th Annual Meeting of the Society of Gynecologic Oncologists in San Diego, CA, 2007.

* Corresponding author. Fax: +1 434 982 1840.
E-mail address: lduska@virginia.edu (L.R. Duska).

0090-8258/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2009.10.069

Interestingly, this unique ovarian histologic subtype has also been shown to have gene expression profiles more similar to clear cell cancers of other organs, such as the endometrium and kidney, than to other types of epithelial ovarian cancers [6]. The clinical behavior of CCC-O is distinct and the prognosis, stage for stage, is worse than that of other epithelial ovarian cancers [4,7–9]. Despite these clinical differences, CCC-O has been managed similarly to the more common epithelial subtypes, including with respect to VTE prophylaxis, both pre- and post-operatively.

The current study was undertaken to document the rate of VTE in CCC-O patients at the Massachusetts General Hospital (MGH) and to compare this to the rate of VTE in similarly staged patients with epithelial ovarian cancer in a case–control study. Furthermore, we tried to identify an at risk population that could potentially be targeted for more aggressive VTE prophylaxis. The potential for payment denial under an extension of CMS 'never-events' was a secondary factor.

Methods

Institutional Review Board approval was obtained for a retrospective record review. All women diagnosed with CCC-O between 1994 and 2004 were then identified from the Massachusetts General Hospital (MGH) pathology tumor registry. Tumors were included that were both pure clear cell histology as well as mixed histology provided that the clear cell component was greater than 10%. Controls with epithelial ovarian cancer without any evidence of clear cell histology were then selected at a two-to-one ratio. Controls were matched to cases for stage, age, and year of diagnosis.

Medical records were abstracted and data regarding histology, stage, body mass index, smoking, co-existing endometriosis, the clinical course of disease, the presence of VTE based on clinical suspicion and subsequent diagnostic testing, and survival were collected. The pathology of all the cases was reviewed by a single Pathologist to confirm the presence of CCC-O. During the time period studied, all patients received peri- and post-operative VTE prophylaxis, including subcutaneous heparin in all patients and heparin plus sequential compression devices in the remainder of patients. Pre-operative heparin consisted of a single dose of unfractionated heparin. Post-operatively patients received either unfractionated heparin 5000 units subcutaneously three times daily or low molecular weight heparin, depending on the clinical algorithm at the time of diagnosis. VTE were diagnosed with the appropriate diagnostic modality (depending on the year of diagnosis) when clinical suspicion arose. All cases and controls were followed until date of death or last clinical follow-up.

Differences between the cases and controls were examined using conditional likelihood score chi-square as well as the exact test using LogXact software (LogXact 5.0.1. Cytel Software Corporation, Cambridge, MA). Conditional logistic regression models available in SAS PROC PHREG were used to examine the association between VTE and CCC-O (SAS System version 8. Statistical Analysis System, SAS Institute, Cary, NC). The relative risk was estimated by the conditional odds ratio. The effects of histology, VTE and stage on survival were examined by using stratified Kaplan–Meier analysis and Cox's proportional hazards regression. Results were considered statistically significant if the P value was <0.05. Small numbers and data type precluded multivariate analysis.

Results

Fifty-eight women with CCC-O were identified during the study period. Of these, 43 had complete records available and were included in the analysis. Eighty-six (86) controls matched for age, stage and year of diagnosis were selected. The majority of controls had serous tumors (47%) with the remainder being endometrioid (33%), mucinous (14%), transitional cell (2%), sarcoma (2%) and mixed (2%). The mean follow-up time was 50 months (range 3–132 months) for the entire cohort.

During the study period a standard service-wide approach to heparin prophylaxis was utilized. All patients (cases and controls) received unfractionated heparin on call to the Operating Room. The majority of both cases and controls also wore sequential compression devices (SCDs) during their surgery and in the immediate post-operative period (only one of five participating surgeons during the time period studied did not routinely use SCDs). All patients (cases and controls) were treated with unfractionated heparin post-operatively until discharge until 2002, when a service-wide change was made to low molecular weight heparin in the post-operative period. The heparin prophylaxis chosen was service (not surgeon) dependent and there were no differences between cases and controls as controls were chosen to match cases with respect to year of diagnosis.

The stage at presentation for the cases is shown in Table 1. Most patients with CCC-O (70%) presented with early (stage I or II) disease, with only 30% of patients presenting with advanced (stage III or IV) disease. The clinical characteristics of the cases and controls are shown in Table 2. Eighty-six controls were matched with 43 cases as planned. There were no significant differences across patients matched for age, stage, and year of diagnosis. Ninety-one percent of patients in both cases and controls received adjuvant chemotherapy. Eleven controls and no cases had a history of smoking.

Eighteen of 43 (42%) of patients with CCC-O experienced VTE, compared with 19 of 86 (22%) of controls ($p=0.024$, OR = 2.5 CI 1.1504–5.60). In patients with CCC-O, 3 (17%) of the VTE were diagnosed at the time of cancer diagnosis, 9 (50%) were diagnosed in the post-operative period (the first 30 days after surgery), and 6 (33%) at the time of tumor recurrence or progression. The controls developed clotting at the following time periods: 31% at the time of diagnosis, 32% in the post-operative period, and 37% with progression or recurrence. With respect to specific type of VTE: 5 patients had PE, 10 patients had DVT, and 3 patients presented simultaneously with both PE and DVT in the CCC-O group. In the control group, 6 patients had PE, 10 patients had DVT, and 2 patients simultaneously had both.

In patients with CCC-O, VTE was twice as common in late-stage disease (8 of 13, 62%) than in early stage disease (10 of 30, 33%) ($p=0.085$) though this was not statistically significant. Controls with non-clear cell histology also had twice the rate of VTE in late stage disease as in early disease, though the number of events was far lower, with 9 of 60 (15%) in early stage disease and 10 of 26 (38%) in late stage disease ($p=0.016$). Considering all pts, late stage was more likely associated with VTE (18 of 39, 46%) vs. early stage (19 of 90, 21%), $p=0.004$.

The majority of patients with CCC-O had endometriosis incidentally found at the time of their cancer surgery and confirmed on pathology review. This was in sharp contrast to the control patients (70% *vs.* 20%, $p<0.0001$). While more VTE were seen in those CCC-O patients with endometriosis than without (47% vs. 31%, $p=0.52$), this did not reach clinical significance. The presence of endometriosis increased the risk of clear cell histology, Odds Ratio (OR) 4.7 [95% CI 1.1, 19.4], $p<0.001$. However, when the data were controlled for the presence of endometriosis, CCC-O was still significantly associated with VTE, OR 2.5 [95% CI 1.2, 5.6], $p=0.019$.

The mean BMI of patients with CCC-O and VTE was 25.5, compared with 28 in patients that did not have VTE ($p=0.2$). Body mass index (BMI) was not related to the presence of VTE. There was also no association between smoking and the presence of VTE, although none of the patients with CCC-O in this series had a history of smoking.

Table 1
Distribution of patients with CCC-O by stage and number of VTE.

Stage	#	%	VTE (#)	% Per stage	% Total VTE
1	15	35%	4	26.7%	22.2%
2	15	35%	6	40.0%	33.3%
3	9	21%	7	77.8%	38.9%
4	4	9%	1	25.0%	5.6%