Gynecologic Oncology 132 (2014) 556–559

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Thrombocytosis at secondary cytoreduction for recurrent ovarian cancer predicts suboptimal resection and poor survival

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HIGHLIGHTS

- Epithelial ovarian cancer (EOC) patients who undergo secondary tumor debulking with a preoperative thrombocytosis have a shortened overall survival.
- Preoperative thrombocytosis is associated with failure to achieve microscopic residual disease at time of secondary tumor debulking.
- Preoperative thrombocytosis is an independent prognostic factor for patients with recurrent EOC who undergo secondary cytoreduction.

ARTICLE INFO

Article history:
Received 14 November 2013
Accepted 4 January 2014
Available online 11 January 2014

Keywords:
Secondary debulking
Thrombocytosis
Ovarian carcinoma
Peritoneal carcinoma

ABSTRACT

Objectives. A growing body of evidence supports a role for thrombocytosis in the promotion of epithelial ovarian cancer biology. However, studies have only linked preoperative platelet count at time of initial cytoreductive surgery to clinical outcome. Here, we sought to determine the impact of elevated platelet count at time of secondary cytoreductive surgery (SCS) for recurrent disease.

Methods. Under an IRB-approved protocol, we identified 107 women with invasive epithelial ovarian cancer who underwent SCS between January 1997 and June 2012. We reviewed clinical, laboratory, and pathologic records from this retrospective cohort. The data was analyzed using the chi-squared, Fisher's exact, Cox proportional hazards, and Kaplan–Meier tests. We defined thrombocytosis as a platelet count $\geq 350 \times 10^9$/L and optimal resection at SCS as microscopic residual disease.

Results. Thirteen of 107 women (12%) with recurrent ovarian cancer had thrombocytosis prior to SCS. Preoperative thrombocytosis at SCS was associated with failure to undergo optimal resection ($p = 0.0001$). Women with preoperative thrombocytosis at time of SCS demonstrated shorter overall survival (33 months) compared to those with normal platelet counts (46 months, $p = 0.004$). On multivariate analysis, only preoperative platelet count retained significance as an independent prognostic factor ($p = 0.025$) after controlling for age at SCS ($p = 0.90$), disease free interval from primary treatment (0.06), and initial stage of disease (0.66).

Conclusions. Elevated platelet count at time of SCS is associated with suboptimal resection and shortened overall survival. These data provide further evidence supporting a plausible role for thrombocytosis in aggressive ovarian tumor biology.

Introduction

Epithelial ovarian cancer is an aggressive malignancy with various histologic subtypes. This year alone there will be 14,030 deaths due to ovarian cancer in the United States largely due to advanced stage of disease at presentation in 70% of women with five-year overall survival of approximately 30% [1,2]. Despite a high rate of remission following primary treatment of advanced stage disease with both surgery and chemotherapy, recurrence is common with more than 60% of advanced stage patients developing recurrent disease [3]. In counseling patients with recurrent tumor, secondary tumor debulking is a potential treatment option depending on various factors including disease free interval, platinum sensitivity, tumor burden, and performance status. Those patients who undergo complete cytoreduction at the time of secondary tumor debulking will benefit the most [3–8]. Good performance status and absence of ascites are predictors of complete surgical cytoreduction in recurrent platinum sensitive epithelial ovarian cancer [9]. At this time, there is still controversy as to which patients with recurrent epithelial ovarian cancer are the best candidates for secondary tumor debulking.

A growing body of evidence supports a role for thrombocytosis in the promotion of cancer biology. Platelets are associated with metastasis, angiogenesis, and tumor cell proliferation [10,11]. In ovarian cancer

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http://dx.doi.org/10.1016/j.ygyno.2014.01.003

models, evidence indicates the existence of a paracrine circuit in which tumor growth is fostered by a paraneoplastic thrombocytosis driven by thrombopoeitic cytokines [12].

Thrombocytosis has been shown to be an unfavorable prognostic factor in a number of solid tumors including colorectal, breast, pancreatic, and lung cancer [13–17]. In advanced stage ovarian cancer, thrombocytosis at the time of initial staging surgery has been linked to worse prognosis including decreased disease free interval, shorter overall survival, and a greater likelihood of suboptimal resection [18,19]. In addition, thrombocytosis in early stage epithelial ovarian cancer has been linked to an eight-fold increase risk of recurrence [20]. Despite the available literature regarding thrombocytosis at the time of primary surgical debulking, it is unclear if thrombocytosis at the time of recurrence has clinical significance.

If a patient is a candidate for secondary debulking at the time of recurrence, thrombocytosis may provide important prognostic information. We hypothesize that thrombocytosis negatively influences tumor biology throughout the disease course. In this study, we evaluate the association between preoperative thrombocytosis, survival, and other clinic-pathologic factors in women with epithelial ovarian cancer undergoing secondary cytoreductive surgery (SCS).

Methods

Under an IRB-approved protocol, we identified 107 women with invasive epithelial ovarian cancer who underwent SCS between January 1997 and June 2012. Patients with a history of invasive epithelial or primary peritoneal carcinoma who underwent secondary tumor debulking at Cedars-Sinai Medical Center in Los Angeles, CA were included in this study. Patients with a tumor of low malignant potential were excluded from this study. In general, patients were considered candidates for secondary tumor debulking if they had a disease free interval greater than six months, Gynecologic Oncology Group performance status less than two, and three sites or less of suspected disease recurrence. All patients underwent secondary tumor debulking by a gynecologic oncologist with the intent of optimal tumor cytoreduction. Patients undergoing palliative surgical procedures were excluded from this study. Following first line chemotherapy, no patient underwent chemotherapy prior to SCS. After secondary debulking all patients underwent treatment with chemotherapy, receiving either a platinum couplet or single agent platinum. A preoperative automated complete blood count within sixty days of surgery was available for all patients. Thrombocytosis was considered as a platelet count $\geq 350 \times 10^9$/L consistent with published criteria [14–16]. Optimal resection at SCS was considered microscopic residual disease. Suboptimal resection was based on residual tumor burden. The following data was abstracted: stage of disease, age at time of SCS, platelet level at time of initial staging surgery, disease free interval from time of initial treatment, platelet level at time of SCS, residual tumor at time of SCS, and overall survival. Differences in clinical and histopathologic factors between patients with and without thrombocytosis were examined with chi-squared and Fisher's exact test. The Cox proportional hazards model was used to assess the significance of potential prognostic factors as predictive parameters for patient survival. Survival probabilities were analyzed with Kaplan–Meier curves. A p-value of 0.05 was considered to be statistically significant.

Results

Of the 107 women with recurrent epithelial or primary peritoneal ovarian cancer who underwent SCS, 13 (12%) had preoperative thrombocytosis (a platelet count $\geq 350 \times 10^9$/L) at the time of SCS. The median age for women with a preoperative thrombocytosis was 65 years old (range 51–83) while those without elevated platelets had a median age of 53 years old (range 36–75). Women with thrombocytosis had a median platelet count of 416×10^9/L (range 352–527). Three of these 13 (23%) patients also had thrombocytosis at their initial staging surgery. Of 55 women with available preoperative platelet counts at initial staging surgery, 18 (33%) had thrombocytosis at that time and subsequently had normal platelet counts prior to SCS. Women without thrombocytosis at SCS had a median platelet count of 243×10^9/L (range 84–338).

Of the 13 patients with a preoperative thrombocytosis at the time of SCS, 11 (85%) were stage III or IV, while 78 (83%) of patients without preoperative thrombocytosis had advanced stage disease. Median disease free interval following primary surgery for those with thrombocytosis at the time of SCS was 21 months (range 8–171) while women who had a normal platelet count prior to SCS had a median disease free interval of 34 months (6–311) after their initial surgery (Table 1).

Of those patients with thrombocytosis at time of SCS, 4 patients (31%) underwent resection to less than 1 cm residual tumor while 9 patients (69%) underwent suboptimal tumor debulking. In contrast, 62 patients (66%) with a normal preoperative platelet count had microscopic residual disease, 25 patients (27%) underwent debulking to less than 1 cm residual disease, and only 7 patients (7%) had suboptimal tumor debulking. Preoperative thrombocytosis at SCS was strongly associated with failure to undergo optimal resection ($p = 0.0001$) (Fig. 1).

Women with preoperative thrombocytosis at time of SCS had a shorter overall survival (median 33 months) compared to those with a normal platelet count (median 46 months) ($p = 0.004$). Overall survival was defined as time from SCS to death (Fig. 2). When examining platelet count as a continuous variable, univariate analysis identified a significant correlation with survival with a relative risk of 1.004 (1.0005–1.0069, $p = 0.02$). On multivariate analysis, only preoperative platelet count retained significance as an independent prognostic factor ($p = 0.025$) after controlling for age at SCS, disease free interval from primary treatment, and initial stage of disease (Table 2).

Discussion

To our knowledge this is the first study to evaluate the significance of thrombocytosis at the time of recurrence of ovarian carcinoma. Prior studies have demonstrated an association between thrombocytosis and poor clinical outcome at the time of initial treatment. With a high likelihood of recurrent disease in advanced stage ovarian cancer, understanding the significance of thrombocytosis in this setting may assist clinicians in counseling patients regarding treatment options. Elevated platelet count at time of SCS is associated with suboptimal resection and shortened overall survival. This data provides further evidence supporting a plausible role for thrombocytosis in aggressive ovarian tumor biology.

Interestingly, eighteen of twenty-one patients with thrombocytosis at initial staging surgery did not have thrombocytosis at the time of SCS. In comparison, only three of thirteen patients with thrombocytosis at SCS had thrombocytosis at the time of initial staging. This may be for various reasons. Firstly, bone marrow may be negatively impacted by

Table 1
Patient characteristics by group.

	Thrombocytosis[a] (n = 13)	Normal platelets (n = 94)
Age at SCS[b], median	65 (range 51–83)	53 (range 36–75)
DFI[c] after primary surgery, median in months	21 (range 8–171)	34 (range 6–311)
Platelets, median	416 (range 352–527)	243 (range 84–338)
Stage I/II	2	16
Stage III/IV	11	78

[a] Thrombocytosis defined as preoperative platelet count $\geq 350 \times 10^9$/L.
[b] Secondary cytoreductive surgery (SCS).
[c] Disease free interval (DFI).