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Platelet effects on ovarian cancer

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Abstract

Growing understanding of the role of thrombocytosis, high platelet turnover, and the presence of activated platelets in the circulation in cancer progression and metastasis has brought megakaryocytes into focus. Platelet biology is essential to hemostasis, vascular integrity, angiogenesis, inflammation, innate immunity, wound healing, and cancer biology. However, before megakaryocyte/platelet-directed therapies can be considered for clinical use, understanding of the mechanism and biology of paraneoplastic thrombocytosis in malignancy is required. Here, we provide an overview of the clinical implications, biological significance, and mechanisms of paraneoplastic thrombocytosis in the context of ovarian cancer.

Introduction

Epithelial ovarian cancer is the fifth leading cause of cancer-related death among women and is the most lethal gynecologic malignancy. An estimated 22,000 women are diagnosed with, and 14,000 women die from this disease annually [1]. Patients diagnosed at stage I-II have a 5-year overall survival rate of 91%. However, because reliable, prospective screening biomarkers are lacking, disease onset is insidious, and late diagnosis of advanced disease is common [2]. Surgical techniques and chemotherapy regimens developed through multiple clinical trials over the past 3 decades have resulted in improvements in ovarian cancer treatment [3, 4]. The median survival time for women with advanced ovarian cancer has improved by 1.6 years in the past 30 years [1, 5]. Evidence from several randomized

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controlled clinical trials has established tumor debulking surgery followed by treatment with a platinum-paclitaxel combination regimen as first-line therapy for advanced ovarian cancer, yielding response rates of more than 80% [3, 4, 6-11]. However, most of these patients eventually relapse and recurrence remains an essentially terminal event [1]. In the setting of recurrent, platinum-resistant ovarian cancer, second-line cytotoxic agents have a 15-20% response rate with virtually no cures [5].

This poor prognosis necessitates the development of more efficacious therapeutic options for women with epithelial ovarian cancer, both in the first-line and recurrent disease settings. It has become clear that interactions between tumor cells and the surrounding microenvironment are critical for tumor biology. Recent evidence indicates that platelets are present in the tumor microenvironment and could play important roles in stimulating tumor growth. Paraneoplastic thrombocytosis is a well-recognized and prevalent phenomenon in patients with ovarian cancer and the mechanisms and biology underlying this event are increasingly important to understand. Here, we provide an overview of the clinical implications, mechanism, and biological significance of paraneoplastic thrombocytosis in the context of ovarian cancer. We will highlight gaps in our existing knowledge, discuss possible therapeutic strategies to target platelets and explore evidence for use of platelets and platelets derived growth factors as biomarkers in ovarian cancer.

Clinical significance of paraneoplastic thrombocytosis in ovarian cancer

Approximately one-third of women with newly diagnosed ovarian cancer have platelet counts exceeding 450,000/ μ L [12]. In addition to arising in a substantial proportion of patients with ovarian cancer, thrombocytosis is associated with several aggressive clinical features including advanced-stage disease, increased median preoperative serum CA-125 levels, and significantly decreased progression-free and overall survival (2.62 years compared with 4.65 years in those without thrombocytosis) [12]. Two separate studies using a multivariate model that included age, disease stage, tumor grade, histologic type, and extent of surgical cytoreduction showed that thrombocytosis remained an independent predictor of compromised survival [12, 13]. These findings are supported by those of Li and colleagues, who identified statistically significant associations between thrombocytosis and advanced stage-disease, high-grade tumors, and elevated CA-125 levels in 183 patients with invasive epithelial ovarian and primary peritoneal carcinomas [14]. This study and a smaller investigation by Menczer and colleagues also demonstrated that thrombocytosis may signify an increased risk of suboptimal surgical cytoreduction and is an independent poor prognostic factor [15]. A retrospective analysis of 107 women with recurrent ovarian cancer showed that thrombocytosis at the time of secondary cytoreductive surgery is associated with suboptimal resection and shortened overall survival [16].

Hypercoagulability and Venous Thromboembolism in ovarian cancer

Venous thromboembolism (VTE) complicates the treatment course of up to 25% of patients with ovarian cancer and is a poor prognostic factor (Table 1) [17, 18]. “Virchow’s triad,” the functional triad of vascular endothelial injury/dysfunction, stasis, and hypercoagulability that mediates the pathogenesis of thrombosis happens often in the setting of ovarian cancer.

Direct injury to the vessel wall can also be inflicted by extrinsic factors such as chemotherapy [19]. A large tumor burden or massive ascites characteristic of ovarian cancer can compress pelvic veins and induce venous stasis, which may predispose patients to VTE. Additionally, venous stasis is an inevitable risk in ovarian cancer patients undergoing surgery secondary to prolonged operative time and a protracted postoperative course. Furthermore, accumulating evidence suggests that cancer in general, and ovarian cancer in particular, leads to an exceptionally hypercoagulable state [20]. Tumors induce platelet production of thrombin, stimulate the coagulation cascade to produce von Willebrand factor and stimulate protease activated receptors on both platelets and endothelial cells [21-23].

These factors likely contribute to the increased number and reactivity of circulating platelets related to VTE in patients with ovarian cancer. Thrombocytosis is associated with VTE in ovarian cancer and is an independent predictor of increased mortality in women who do develop a thrombus [12].

Mechanisms of paraneoplastic thrombocytosis in ovarian cancer

Numerous cytokines, such as thrombopoietin (TPO) and various interleukins, have been implicated in megakaryopoiesis and platelet production, many having additive or synergistic effects at various stages in the process. It is estimated that TPO stimulates the growth of 75% of all human megakaryocyte progenitor cells [24]. There is a long-noted relationship between certain chemokines and thrombocytosis in the setting of malignancy. Thrombocytosis has been associated with elevated levels of TPO in patients with hepatocellular carcinoma [25]. In one study of patients with colorectal cancer, significantly higher platelet counts and plasma TPO levels were identified in patients with stage III compared to patients with stage I disease [26]. It has also been demonstrated that serum IL-6 levels are significantly correlated with platelet count in patients with renal cell carcinoma [27].

Although these correlations were observed, the exact mechanism of paraneoplastic thrombocytosis was unknown until recently [12]. A multicenter study of 619 patients with epithelial ovarian cancer showed that thrombocytosis is associated with elevated plasma levels TPO and interleukin-6 (IL-6) in patients with ovarian cancer [12]. In accompanying orthotopic mouse models of ovarian cancer, tumor-derived IL-6 stimulated hepatic thrombopoietin synthesis and paraneoplastic induction of thrombocytosis. These findings provide important evidence that the paracrine circuit of increased hepatic TPO synthesis in response to tumor-derived IL-6 is an underlying mechanism of paraneoplastic thrombocytosis in ovarian cancer (Figure 1).

Biological significance of paraneoplastic thrombocytosis in ovarian cancer

Platelets are host components that can be co-opted into facilitating the growth and dissemination of ovarian cancer. Platelets have been shown to play a role in tumor growth, tumor metastasis and angiogenesis.

Ovarian cancer cells adhere to and activate platelets to increase proliferation that can occur even without direct contact [16]. Both activated platelets and platelet releasate increases

cancer cell invasion [28]. Platelet contents may be released into the peritumoral space following platelet activation and may enhance tumor cell proliferation, metastasis and extravasation [29-33]. The proliferation effects are mediated in part by transforming growth factor beta (TGF- β -1). Cancer cells secrete IL-6, which directly and indirectly (*via* liver TPO production) stimulates bone marrow megakaryocyte and platelet production of TGF- β 1. TGF- β 1 produced by platelets activates the TGF- β 1/Smad pathway in tumor cells, enhancing proliferation and metastasis. Direct contact between cancer cells and platelets activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway, synergizing with TGF- β 1/Smad to induce epidermal-to-mesenchymal transformation, extravasation, invasion and metastasis [34]. Platelets have been reported to extravasate into ascites and rapidly adhere to free floating cells in tumor bearing mice [12]. This is a noteworthy finding because ovarian cancer often spreads within the peritoneal cavity, and platelets in ascites would provide direct opportunities for interactions. The exact mechanism by which platelets promote peritoneal metastasis through the ascites is not fully understood.

Angiogenesis is known to be required for tumor growth; to allow delivery of proteases and cytokines that permit cancer progression. Tumor vasculature develops due to an altered balance between angiogenesis stimulators and inhibitors released by the tumor microenvironment. Pro- and anti-angiogenic mediators are packaged into distinct alpha granules within the platelets and are released during the formation of tumor cell-platelet emboli based on the selective engagement of platelet receptors [35]. PAR-1 activation is associated with VEGF release and suppression of endostatin, while PAR-4 activation, conversely, stimulates endostatin release and suppresses release of VEGF [36]. In addition to increasing tumor cell proliferation, migration and metastasis, platelets support vascular pericytes, and promote tumor endothelial cell survival, which may also contribute to platelet enhancement of tumor angiogenesis [12]. The source and mechanism of platelet derived angiogenesis remains under active investigation in ovarian cancer.

In vitro data suggest that platelets may also play a role in chemoresistance in ovarian cancer. Human platelets increased the survival of colonic and ovarian adenocarcinoma cells treated with 5-fluorouracil and paclitaxel. These effects may be mediated by the release of the chemokine RANTES, thrombospondin-1, TGF- β and clusterin [37]. Platelet derived growth factor alpha is a class III receptor tyrosine kinase that plays a crucial role in tumor growth and survival via inhibition of apoptosis signaling [38]. A large percentage of tumors with epithelial ovarian carcinoma have been reported to express PDGFR α (56-97%) [39, 40]. In an orthotopic mouse model, PDGFR α blockade with a neutralizing antibody enhanced the antitumor activities of taxanes in ovarian carcinoma [41].

Targeting platelets as a therapeutic strategy in ovarian cancer

IL-6 is considered a therapeutic target due to its roles in tumor angiogenesis, inflammation, and stimulation of paraneoplastic thrombocytosis [12]. Directly inhibiting IL-6 levels using anti-IL6 therapy has been studied in ovarian cancer. Stone *et al.* showed that treatment with an IL-6 targeted antibody, siltuximab, blocked thrombocytosis in an orthotopic mouse model of ovarian cancer. Moreover, combination of siltuximab and paclitaxel was more effective

than paclitaxel in reducing tumor growth. In the same study, patients treated with siltuximab every 2 weeks showed normalization of platelet counts after 3 weeks of treatment. A total of eight patients achieved radiological disease stabilization, which lasted 6 months or more in 4 cases. One of these 8 also had normalization of CA125 that lasted for 12 weeks, giving an overall partial response by combined RECIST/CA125 criteria. [42]. Tocilizumab is another IL-6 inhibitor (IL-6i) but has not been studied in ovarian cancer. Other agents targeting either IL-6 or its receptor remain under investigation [43].

Directly targeting thrombopoietin synthesis or the development of thrombopoietin receptor (TPO-R) antagonists may be another approach, however, their role in the context of treating paraneoplastic thrombocytosis remains to be established.

Several prospective clinical trials have shown that low-molecular-weight-heparin (LMWH) improves survival in cancer patients with various tumor types [44-47]. Whether this is based on a reduction in fatal pulmonary embolisms, an inhibition of tumor progression or another mechanism is not known and whether an antineoplastic effect exist specifically in ovarian cancer is also not known. A phase II trial showed that dalteparin, a type of LMWH, was safe to use and well tolerated in patients with epithelial ovarian cancer; however, the lack of a control group precluded any inference about antineoplastic effects or a survival benefit of dalteparin [48].

In preclinical models, correction of thrombocytosis with anti-platelet antibody reduces tumor growth and promotes tumor necrosis. Therefore, megakaryocyte targeted treatment could provide a significant benefit for patients with ovarian cancer. Directly targeting important growth factors released by platelets could also be of value. TGF- β 1 is expressed in majority of epithelial ovarian cancers [49]. Inhibition of TGF- β 1 was shown to inhibit proliferation of ovarian cancer cells *in vitro* despite co-incubation with platelets [50].

Non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 inhibitors (COXIBs) may also be effective for inhibiting cancer formation and progression [51]. These drugs have not been studied specifically for the treatment of ovarian cancer but may have a role in cancer prevention [52]. NSAIDs and COXIBs may help suppress thrombocytosis by preventing PGE₂ synthesis [51]. Clinical data have demonstrated a reduction in the development of cancer precursor lesions as well as cancer incidence and mortality rates after regular administration of such drugs in patients with colorectal cancer [53, 54]. Recent data support the hypothesis that these benefits extend to a much broader spectrum of malignancies, including ovarian cancer [55]. A meta-analysis of pooled data from 12 population-based case-control studies of ovarian cancer, including 7776 cases patients and 11,843 control subjects accrued between 1992 and 2007 showed that aspirin use was associated with a reduced risk of developing ovarian cancer, especially among daily users of low-dose aspirin. Results were similar but not statistically significant for non-aspirin NSAIDs, and no association was found between acetaminophen use and risk of developing ovarian cancer [55]. These findings suggest that aspirin could reduce the risk of ovarian cancer by 20-34% depending on the dose and frequency of use.

Platelets as biomarkers in ovarian cancer

It has been well-established that paraneoplastic thrombocytosis is associated with adverse clinical outcomes in ovarian cancer. However, the use of platelets as a biomarker for disease surveillance or progression has not been well studied in ovarian cancer [13]. A recent retrospective analysis of patient platelet counts at time of initial diagnosis and time of recurrence showed that patients with normal CA-125 at the time of recurrence had a 49% increase in platelet counts compared with levels at initial diagnosis, suggesting that platelets may be a potential biomarker for disease recurrence [56].

Summary

In summary, there is growing evidence that platelets play a profound role in ovarian cancer growth and progression. Paraneoplastic thrombocytosis results from a complex paracrine circuit between the tumor and host. Specifically, this process is facilitated by hepatic TPO synthesis that arises in response to tumor derived IL-6; thus increasing platelet counts, which in turn promotes tumor growth and produces a positive feedback loop [12]. This aberrant paracrine signaling has important clinical consequences because one-third of women diagnosed with ovarian cancer have thrombocytosis and are therefore at increased risk for VTE as well as compromised disease-specific survival [13]. Countering paraneoplastic thrombocytosis using direct antiplatelet strategies has the potential to serve as a valuable prevention and therapeutic approach in ovarian cancer patients. Moreover, platelets may be useful as potential biomarkers for disease surveillance. Paraneoplastic thrombocytosis in ovarian cancer is not simply an epiphenomenon, but an important contributor to tumor progression.

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Figure 1.

Mechanism of Paraneoplastic Thrombocytosis in Ovarian Cancer

The paracrine signaling pathway that mediates paraneoplastic thrombocytosis in epithelial ovarian cancer. Interleukin-6 secreted by ovarian cancer cells stimulates hepatic thrombopoietin production. This drives thrombopoiesis in the bone marrow, giving rise to thrombocytosis. "Reprinted with permission" [12]

Table 1

Venous Thromboembolism (VTE) in Ovarian Cancer

Histologic Subtypes	Number of VTE/total patients	Timing of VTE	Factors Associated with increased risk of VTE*	Impact on survival	Reference
All	18/72 (25.0%)	All cases at time of diagnosis	Clear cell histology* Massive ascites*	Not examined	[57]
All	19/86 (22.1%)	At diagnosis: 6 (31.6%); perioperative: 6 (31.6%); during long-term follow-up: 7 (36.8%)	Stage	Not examined	[58]
All	42/253 (16.6%)	At diagnosis: 8 (19.0%); perioperative: 6 (14.3%); during initial treatment: 16 (38.1%); during long-term follow-up: 12 (28.6%)	Prior VTE Age Stage Suboptimal Transabdominal Radical Surgery (TRS)* Body mass index*	Not examined	[59]
Epithelial	57/559 (10.2%)	All cases perioperative	Stage Ascites Suboptimal TRS	No impact	[60]
All	672/13,031 (5.2%)	Perioperative: 257 (38.2%)	Age* Stage*	Reduced	[61]
All	76/2,743 (2.8%)	Preoperative and during initial treatment: 38 (50.0%)	Age* Body mass index > 30 kg/m ² *	Reduced	[62]
All	128/12,835 (1.0%)	All cases predated diagnosis of ovarian cancer	Stage	Reduced	[63]

* In multivariate analysis