Thrombocytosis in Advanced Epithelial Ovarian Cancer

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Objective: *Thrombocytosis (platelet count greater than 400,000 /mm^3) has been identified as a poor prognostic factor in many cancers. The objectives of the present study were to determine the incidence of thrombocytosis in advanced epithelial ovarian cancer and the cut off point level of platelet count in Thai patients determining thrombocytosis condition and association between survival time in both thrombocytosis condition (platelet count greater than 400,000 /mm^3 and 305,000/mm^3).*

Design: *Descriptive study*

Material and Method: *One hundred and twenty epithelial ovarian cancer patients were included between January 2004 and December 2005. Their medical records were retrospectively reviewed and data was analyzed using χ^2, Fisher's exact test, and Student t- test. The level of platelet counts determining thrombocytosis condition in Thai patients were record and analyzed by ROC curve. Survival was analyzed by the method of Kaplan and Meier.*

Results: *When using the standard criteria of thrombocytosis (platelet counts greater than 400,000 /mm^3), the incidence was 35% (42/120 cases). Among advanced-stage patients, such incidence was 56.7% (42/74 cases). The criteria for diagnosis of thrombocytosis in the present study was platelet counts greater than 305,000/ mm^3. When using such criteria, the overall incidence of thrombocytosis was 49.1% (59/120 cases) and was 72.97% (54/74 cases) in advanced stage. Patients with preoperative thrombocytosis were found to have higher CA - 125 level, greater prevalence of ascites, and worse prognosis.*

Conclusion: *The incidence of thrombocytosis in Thai patients with advanced epithelial ovarian cancer was 56.7% and 72.9% when using platelet count level greater than 400,000 /mm^3 and 305,000/mm^3 respectively, which was higher than that of the early stage. This implies that thrombocytosis is probably a marker of cancer aggressiveness.*

Keywords: *Thrombocytosis, Advanced stage, Epithelial ovarian cancer*

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Thrombocytosis (platelet counts greater than 400,000/mm^3) has been reported in a variety of solid tumors[1,2], including lungs, renal, gastric, breast, pancreatic, and colon malignancies. In gynecologic cancers, pre-operative elevations of platelet counts have been described for endometrial, vulvar, and cervical cancer[3-8]. A few studies suggest that thrombocytosis may be an independent poor prognostic factor in locally advanced cervical carcinoma[8]. In epithelial ovarian cancer, association between thrombocytosis and survival has been inconsistent due to more limitation. The etiology of neoplastic megakaryocytosis remains unclear. The pathophysiology appears to be related to an increased rate of platelet production[1,2,9].

Thrombopoietein (TPO) is thought to be the primary physiologic regulator involved in the regulation of megakaryopoiesis as well as platelet production. Two possible mechanisms of thrombopoiesis were action at TPO receptor or feedback control at level of TPO mRNA in bone marrow[10-14]. Malignant cells produce cytokines such as IL-6, IL-1 and other growth factors capable of inducing platelet production. Preoperative thrombocytosis may favor a diagnosis of

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malignancy in women undergoing surgical evaluation of pelvic mass[15,16]. While these data indicate that thrombocytosis may be a marker reflective of tumor burden, other studies suggest that platelets may contribute to tumor growth and metastases.

Thrombospondin is an adhesive glycoprotein (P-selection) that supports the adhesion of tumor cells to endothelium, and may promote metastasis of tumor cell[17,18]. In 2004, Andrew J Li,et al showed that thrombocytosis in epithelial ovarian cancer reflects more than tumor burden, elevated platelet counts may function in ovarian cancer growth and metastasis, and may contribute to a more aggressive tumor biology. It is associated with poor survival outcome and poor clinicopathologic prognostic factors[19]. In Asian countries such as Thailand, there has been no study on thrombocytosis in epithelial ovarian cancer, thus, the authors have hypothesized that thrombocytosis may depend on difference in race, socioeconomic status, and foods, etc. There may be difference in the incidence between thrombocytosis condition in advanced epithelial ovarian cancer and the thrombocytosis condition in Thai patients. This difference may be the cut-off point level of platelet counts.

Material and Method

From January 2004 to December 2005, 120 epithelial ovarian cancer platelets underwent primary treatment at Bhumibol Adulyadej Hospital. Patients with tumors of low malignant potential and any histories of myeloproliferative disorders, acute inflammatory disease, or spleenectomies were excluded from the present study. All patients underwent primary surgical staging by gynecologic oncologists with the intent of optimal tumor cytoreduction, no patient underwent neoadjuvant chemotherapy. Pelvic lymph node resection was performed in every patient. Following surgical staging, patients received platinum-based chemotherapy as indicated.

A pre-operative automated complete blood count within 14 days of surgery was available for all patients. Consistent with published criteria, it is considered as thrombocytosis when the platelet count is greater than 400,000 /mm^3. Patients' data were retrospectively collected from cancer records designed by the authors department.

The following data were collected; pre-operative platelet counts, pre-operative Hb level, pre-operative CA-125 level, stage (by FIGO staging), histology, optimal or suboptimal tumor cytoreduction, pre-operative monocyte counts, preoperative WBC counts, ascites in patient (qualitative), intra-operative blood loss, and patient status (alive with disease, alive without disease, death with disease, or death with other disease).

Differences in clinical and histopathological factors between patients with and without thrombocytosis were tested with the χ^2 for comparing categorical variables or Fisher's exact test and student's t-test for comparing between two means. Survival of patients with and without thrombocytosis was tested with Kaplan Meier's method with *p*-value of less than 0.05 was considered statistically significant.

The preoperative level of platelet count was used to produce an ROC curve to find the cut-off point of the level that determined thrombocytosis condition. The same data were reanalyzed by using the new level of platelet counts to determine the thrombocytosis.

Results

Among the 120 patients, 42 cases (35%) had thrombocytosis (using platelet counts of greater than

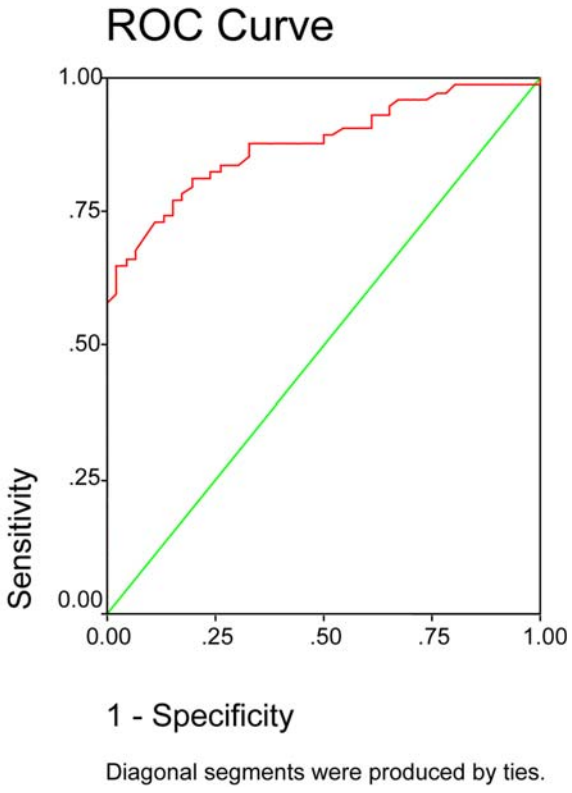

Fig. 1 ROC curve showing cut off point of platelets level between early and advanced stage epithelial ovarian cancer

400,000/mm^3). All of them were in advanced stage (stage III and stage IV). By analyzing the ROC curve, the authors noted the new cut-off point at the level of platelet counts greater than 305,000/mm^3 to determine the thrombocytosis condition (95% CI 0.816-0.937). When we used this new cut-off point, the condition of thrombocytosis in epithelial ovarian cancer patients increased to 59 (49.1%) patients, and to 54 (72.97%) in patients in advanced stage (Fig. 1).

The majority of patients were found to have advanced stage disease at surgery. Seventy-four (61.7%) patients were diagnosed with stage III or stage IV disease, and 46 (38.3%) patients were diagnosed with stage I or II disease. The patient's characteristics such as career, incomes, socio-economic status, parity, and regimen of chemotherapy were significantly not different but the average age of patients with early stage was significantly lower than that of the advanced stage.

The pre-operative platelet counts levels were analyzed by ROC curve. At platelet counts greater than 305,000/mm^3, the sensitivity was 72.97%, and the specificity was 89.13% in predicting advanced stage epithelial ovarian cancer. The accuracy of the test was 79.1%. Instead, when using the level of platelet count greater than 400,000/mm^3, the sensitivity was 56.7% and the specificity was 100%. The accuracy of the test was 73.33% lower than the former.

Association between the presence or absence of thrombocytosis in advanced stage epithelial ovarian cancer and the patients' clinical and histopathological characteristic are shown in Table 1.

Patients with thrombocytosis were found to have significantly greater elevation of pre-operative CA-125 level, more prevalence of ascites, greater pre-operative monocyte count level, greater intra-operative blood loss, and greater post-operative platelet count level. There was no association in the patient's age, pre-operative Hb level and pre-operative WBC level. The factors in the present study as above were the same statistically significant as we used both platelet counts level.

At platelet counts level greater than 400,000/mm^3, 31(73.8%) patients of advanced stage had residual disease greater than 1 cm, and only 11 (26.2%) patients had optimal surgery ($p < 0.05$). Whereas, at platelet counts level lower than 305,000/mm^3, all of the advanced stage patients had optimal surgery (Table 2).

In the present study, patients with thrombocytosis (platelet counts level greater than 305,000/mm^3) had mean survival time significantly shorter than patients without thrombocytosis ($p = 0.017$) 15.62 months (95%CI 12.48-18.76) vs. 22.04 months (95%CI 21.32-22.75), respectively (Fig. 2).

When using platelet count level greater than 400,000/mm^3, patients with thrombocytosis still had mean survival times shorter than patients without thrombocytosis but not significantly different ($p = 0.51$) as shown in Fig. 3.

Discussion

Thrombocytosis is a frequent pre-operative finding in epithelial ovarian cancer patients and may be associated with a more aggressive tumor biology.

Table 1. Association between presence and absence of thrombocytosis in advanced stage epithelial ovarian cancer (platelet greater than 305,000/mm^3) and clinical and histopathologic characteristics

Factors	Platelet counts level (/mm^3)		p-value
	< 305,000/mm^3 n = 20	≥ 305,000/mm^3 n = 54	
- mean age (yrs)	60.55±12.54	62.37±11.22	0.119
- preoperative Hb. Level (g/dl)	12.26±6.1	9.86±5.5	0.110
- preoperative CA-125 level (U/ml)	2,112±315.4	4,392±461.3	<0.05*
- number of patients with ascites	3	48	<0.05*
- preoperative WBC level (/mm^3)	6,676.5±875.6	10,769.8±978.3	0.066
- postoperative platelet counts level (/mm^3)	197,800±90,864	306,657±88,045	0.001*
- preoperative monocyte counts level (/mm^3)	356.5±146.1	745.3±113.3	0.002*
- intraoperative blood loss (ml)	654.0±254.5	1,134.6±224.6	0.016*

Data are mean ± SD

* Statistical significance different: between means

Table 2. Association between thrombocytosis in advanced epithelial ovarian cancer and tumor cytoreducibility

number of patients / Tumor cytoreducibility	Platelet counts level (/mm^3)		p-value
	< 305,000/mm^3	≥ 305,000/mm^3	
Optimal surgery	20 (100%)	21 (38.9%)	
Suboptimal surgery	0 (0%)	33 (61.1%)	-
Total 74 patients	20	54	
number of patients / Tumor cytoreducibility	Platelet counts level (/mm ^{3})		p-value
	< 400,000/mm^3	≥ 400,000/mm^3	
Optimal surgery	30 (93.77%)	11 (26.2%)	
Suboptimal surgery	2 (6.3%)	31 (73.8%)	<0.05
Total 74 patients	32 (100%)	42 (100%)	

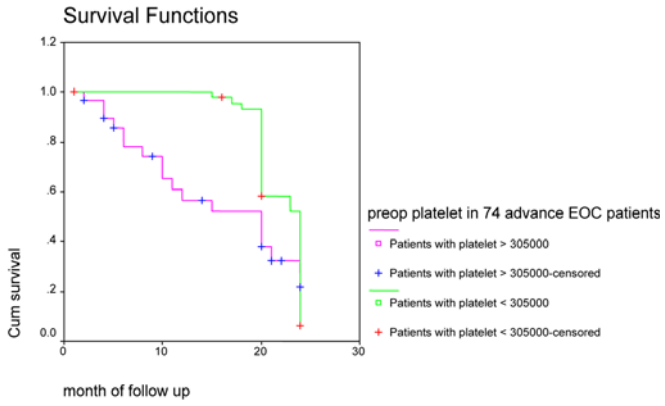

Fig. 2 Survival curve between platelet level ≥ 305,000/mm^3 and platelet level < 305,000/mm3 in advanced epithelial ovarian cancer patients

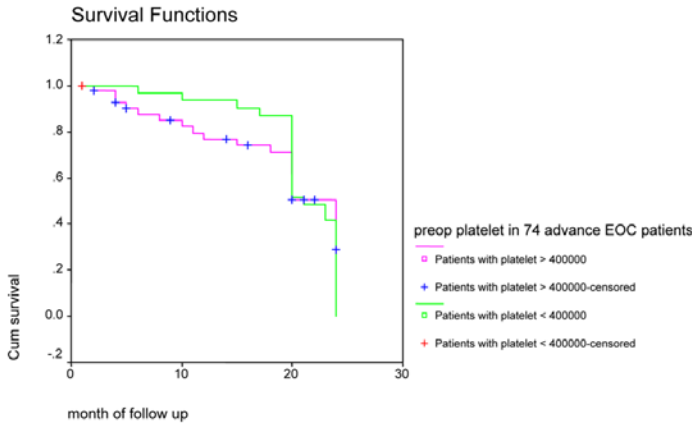

Fig. 3 Survival curve between platelet level ≥ 400,000/mm^3 and platelet level < 400,000/mm3 in advanced epithelial ovarian cancer patients

The authors identified significant associations between thrombocytosis in advanced stage and many poor prognostic factors such as suboptimal cytoreduction, worse patient survival time, greater pre-operative CA-125 levels etc.

The association between thrombocytosis and malignancy has been well demonstrated[1]. Levin and Conley reported in 1964 that nearly 40% of the patients with inoperable cancer had platelet counts greater than 400,000/mm^3[2]. Less data regarding thrombocytosis are available in patients with epithelial ovarian cancer. The authors' findings support those of Andrew J Li et al[19] and Zeimet et al[20] who noted that thrombocytosis was associated with advanced stage disease, higher serum levels of CA-125, greater prevalence of ascites and greater incidence of suboptimal cytoreduction. In the present study of Thai patients, when the platelet counts was analyzed by ROC curve, the new level of cut off point for thrombocytosis was identified which was greater than 305,000/mm^3 (95% CI 0.816-0.937). The accuracy of the platelet count level in detecting the stage of disease was 79.16% at cut-off point level greater than 305,000/mm^3 whereas it was 73.33% at cut off point level greater than 400,000/mm^3. However, the platelet count level of greater than 400,000/mm^3 had higher specificity than the platelet count level of greater than 305,000/mm^3 in detecting advanced stage.

The authors' findings identified a statistically significant association between thrombocytosis (both platelet counts level greater than 305,000/mm^3 and greater than 400,000/mm^3) and tumor cytoreducibility, and confirmed that thrombocytosis was a poor prognosticator. Thrombocytosis was also associated with factors reflective of more aggressive tumor biology, and predicted shorter survival time.

This data was limited by retrospective nature so it cannot confirm a causal relationship between thrombocytosis and tumor aggressiveness. However, the authors' findings showed that thrombocytosis in the presented patients was a negative prognostic factor in advanced epithelial ovarian cancer patients.

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ภาวะเกล็ดเลือดสูงผิดปกติในผู้ป่วยโรคมะเร็งรังไข่ชนิดเยื่อบุผิวระยะลุกลาม

ถนอมศิริ สุนทรธรรม, วีระ สุรเศรณีวงศ์, การุณ เก่งสกุล, เกษม วิจัยธรรม, ภานนท์ เกษมศานต์, สินาท พรหมมาศ

วัตถุประสงค์*: 1. เพื่อศึกษาถึงอุบัติการณ์ของภาวะระดับเกล็ดเลือดสูงผิดปกติในผู้ป่วยโรคมะเร็งรังไข่ชนิดเยื่อบุผิวระยะลุกลาม*

2. เพื่อศึกษาถึงค่าจุดตัดของระดับเกล็ดเลือดที่ใช้บอกภาวะระดับเกล็ดเลือดสูงผิดปกติในผู้ป่วยโรคมะเร็งรังไข่ชนิดเยื่อบุผิว

วัสดุและวิธีการ*: ผู้ป่วยโรคมะเร็งรังไข่ชนิดเยื่อบุผิว 120 คน ตั้งแต่ 1 มกราคม พ.ศ. 2547 ถึง 31 ธันวาคม พ.ศ. 2548 ถูกรวบรวม ข้อมูลย้อนหลัง โดยหาอุบัติการณ์ของภาวะเกล็ดเลือดสูงผิดปกติ (> 400,000/mm^3), และหาค่าจุดตัดของระดับเกล็ดเลือดโดยวิเคราะห์ข้อมูลโดยใช้ ROC curve และนำข้อมูลมาวิเคราะห์หาความสัมพันธ์กับปัจจัยต่าง ๆ โดยใช้สูตรคำนวณทางสถิติ Chi-square test, Fisher's exact test และ Student t test*

ผลการศึกษา*: อุบัติการณ์ของภาวะระดับเกล็ดเลือดสูงผิดปกติในผู้ป่วยโรคมะเร็งรังไข่ชนิดเยื่อบุผิว พบได้ 35 % โดยมีอุบัติการณ์ในผู้ป่วยระยะลุกลาม 56.7% (ระดับเกล็ดเลือด > 400,000/mm^3) เมื่อวิเคราะห์โดยใช้ ROC curve จะได้ค่าจุดตัดที่ระดับเกล็ดเลือด > 305,000/mm^3 ซึ่งจะพบอุบัติการณ์ได้ถึง 49.1% และเป็นระยะลุกลาม 72.97%*

สรุป*: อุบัติการณ์ของภาวะระดับเกล็ดเลือดสูงผิดปกติในผู้ป่วยโรคมะเร็งรังไข่ชนิดเยื่อบุผิวระยะลุกลามสูงถึง 56.7% โดยพบมากกว่าระยะเริ่มแรก ดังนั้นภาวะระดับเกล็ดเลือดสูงผิดปกติจะมีความสัมพันธ์กับความรุนแรงของโรคซึ่งอาจใช้เป็นปัจจัยในการบอกการพยากรณ์ของโรคได้*