Ann Surg Oncol (2017) 24:2259–2265
DOI 10.1245/s10434-017-5834-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Preoperative Thrombocytosis Predicts Shortened Survival in Patients with Malignant Peritoneal Mesothelioma Undergoing Operative Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy

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ABSTRACT

Background. This study was designed to determine the clinical significance of preoperative thrombocytosis in patients with malignant peritoneal mesothelioma (MPM) undergoing operative cytoreduction (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). CRS and HIPEC have been associated with prolonged survival in patients with MPM and is the preferred treatment in select patients. However, patient selection criteria remain ill-defined for this operation that is also associated with significant morbidity and mortality. Preoperative thrombocytosis has been associated with poor outcomes in various malignancies but never studied in MPM.

Methods. Between January 2006 and December 2015, 100 patients with high-grade epithelioid MPM were evaluated and selected for CRS and HIPEC at our center (M: 53, F: 47; mean age: 54 years [range 17–81 years]). We analyzed various patient and treatment related factors potentially associated with overall survival (OS).

Results. The median actuarial overall survival was 32.8 months; the actuarial 1-, 3-, 5-year survivals were 70, 49, and 36%, respectively. On multivariate analysis, suboptimal resection (CCR > 1), high tumor burden (PCI > 20), and elevated preoperative platelet count ($>367{,}000/mm^3$) were independently associated with shortened OS ($P < 0.05$). Median OS in patients with elevated versus normal platelet counts were 13 and 58 months, respectively ($P < 0.001$). Compared with patients with normal platelet counts, patients with elevated counts had significantly greater residual disease after operation ($P = 0.008$).

Conclusions. Elevated preoperative platelet count is independently associated with poor outcome. Notably, thrombocytosis reflects aggressive tumor biology and should be considered a factor in patient selection for CRS and HIPEC.

Malignant peritoneal mesothelioma (MPM) is a rare and ultimately fatal neoplasm that arises from mesothelial cells lining the peritoneum. The incidence of MPM in the United States is estimated to be between 400 and 800 cases annually, with both males and female reporting equal incidence of disease.[1] Patients with MPM most commonly present with abdominal pain, bloating, and/or ascites.[2] Morbidity and mortality are almost always due to regional disease progression in the abdomen rather than distant metastatic spread.[3–5] In patients treated with either chemotherapy or palliative care alone, median overall survival is approximately 6 months.[2,6] Operative cytoreduction (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as the preferred initial treatment in select patients with MPM and is associated with an overall survival between 34 to 92 months.[7–9]

MPM has heterogeneous tumor biology. Although some patients survive for years even with recurrent disease, others will experience rapid tumor recurrence, progression, and death after initial treatment.[10,11] Several patient and treatment-related factors are associated with better

First Received: 25 October 2016;
Published Online: 21 March 2017

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outcomes, including limited extent of disease, lack of deep tissue invasion, optimal cytoreduction, absence of lymph node metastases, low histologic grade, and age <60 years.[7,11,12] Some of these prognostic factors assist with risk stratification for CRS and HIPEC, which has a reported morbidity and mortality of 30% and 2%, respectively.[5,7,13] However, patient selection for initial operation remains ill defined.

In a number of solid tumors, such as colorectal cancer and gynecological malignancies, preoperative thrombocytosis has been identified as an adverse prognostic factor.[14–16] Despite the growing body of evidence supporting thrombocytosis as a negative prognostic factor in several cancers, the clinical significance of preoperative thrombocytosis has never been studied in patients with MPM. Additionally, it is unknown whether thrombocytosis directly predicts poor prognosis or is a surrogate for other prognostic factors, such as disease burden or extent of surgical resection. We investigated the clinical significance of preoperative platelet counts in patients undergoing operative resection for high-grade MPM. We also studied the relationship between preoperative thrombocytosis and other clinicopathological factors to elucidate further the oncologic role of platelets.

PATIENTS AND METHODS

Patients

This study reviews data from 100 patients with histologically proven high-grade epithelioid MPM who underwent operative CRS and HIPEC between January 2006 and December 2015 at our institution. Data review and analysis was conducted with the approval of the Institutional Review Board of the University of Maryland School of Medicine, Baltimore. All patients were assessed clinically as acceptable operative candidates with a disease burden judged amenable to a complete gross cytoreduction based on laparoscopic or radiographic findings.

Patients underwent exploratory laparotomy, lysis of adhesions, cytoreduction, and HIPEC as previously described.[7] The goal of surgery was to render each patient grossly free of disease while attempting to maintain normal digestive function and quality of life after the procedure. Procedures were generally designed to be visceral sparing, that is, performed without an intestinal resection or a permanent end stoma if possible. For the parietal peritoneum, a peritoneal stripping was performed where disease was present, but areas appearing grossly normal were not routinely removed. The pelvic peritoneum was removed without a rectal resection where possible; if a rectal resection was performed then a temporary diverting loop ileostomy was usually created. In postmenopausal women, a hysterectomy and bilateral salpingo-oophorectomy were performed when indicated; in premenopausal women that procedure was performed selectively in an attempt to preserve at least one ovary for endocrine function. Omentectomy with or without splenectomy were almost always performed as omentum is a favored site for disease. The mesentery of the small bowel, liver capsule, and peritoneum over the pancreas were usually treated with local thermal ablation. Diffuse disease on the serosa of the small bowel represented an area of limitation with respect to resection or thermal ablation.

After cytoreduction, HIPEC was administered for 90 min using a closed recirculating system consisting of a reservoir, roller pump, and heat exchanger using either carboplatin ($n = 2$) or mitomycin C ($n = 98$). These agents are commonly administered via HIPEC;[17] they have a nonspecific mechanism of antitumor activity, and they do not have demonstrable toxicity to the normal peritoneal tissues. The perfusion flow rate was maintained at 1.5 L/min primarily to warm the peritoneal tissues using a perfusate volume that varied from 4 to 6 L depending on the size of the potential space of the peritoneal cavity. The peritoneal cavity was warmed to a median temperature of 41 °C, and carboplatin at a dose of 600 mg/m^2 or mitomycin C, 40 mg/m^2, was added to the perfusate. Perfusion was continued for 90 min, during which there was constant, manual agitation of the abdomen to ensure even distribution of the perfusate.

Initial and Follow-Up Evaluation

Before treatment, each patient underwent a physical examination, routine laboratory studies, and a computed tomographic (CT) or magnetic resonance imaging (MRI) scan of the abdomen and pelvis. Preoperative blood samples were obtained within 30 days before operation. For 97 of 100 patients whose preoperative lab work was available, 90 had preoperative labs drawn at our institution. Thrombocytosis was defined as a platelet count of >367,000/mm^3, according to the normal range of our institution (153,000–367,000/mm^3). Intraoperatively, the completeness of cytoreduction (CCR) was assessed as follows: CCR 0, no gross residual disease; CCR 1, fewer than 100 total lesions all <5 mm; CCR 2, more than 100 total lesions all <5 mm or any one >5 mm; and CCR 3, residual tumor >1 cm. Severity of morbidity was assessed using the Clavien-Dindo scale.[18] Generally, patients were evaluated 3 to 6 weeks postoperatively and then every 3 months for 1 year, every 4 months for 1 year, and then every 6 months with blood work, physical examination, and CT of the chest, abdomen, and pelvis to assess for evidence of tumor recurrence.

Histologic Categorization of Tumors

Diagnosis of mesothelioma was confirmed in every patient, including review of pertinent immunohistochemical studies. Tumors were categorized histologically as high-grade due to epithelioid features and evidence of tissue invasion as previously described.[12,19]

Statistical Analysis

The data were reported on an intention-to-treat basis; all patients selected for the procedure were included. The primary objective of analysis was to identify prognostic factors associated with overall survival (OS), which was determined from the time of operation. For each clinicopathological variable, an actuarial analysis was initially performed, using the Kaplan–Meier method with two-tailed log-rank *P* values to evaluate potential prognostic factors. Based on the univariate analyses, a subset of variables was chosen (if $P < 0.05$) to include in a Cox proportional hazards analysis to determine, which, if any, variables were independent predictors of shortened OS. All *P* values were two-tailed. Perioperative mortality was defined as any death that occurred during the same hospital admission and was included in the overall survival analysis for all patients but excluded from the survival analysis of each clinicopathological variable. The relationship between each variable and preoperative platelet count was tested by Chi square test. All statistical analyses were performed with the Statistical Package for Social Sciences for Windows (Version 22.0; IBM SPSS statistics, Armonk, NY).

RESULTS

Patient demographics and clinical data are shown in Table 1. Gender distribution within our cohort was approximately equal (53% men and 47% women) and the mean age at time of operation was 54 years. In the 100 patients, the mean peritoneal cancer index (PCI) was 23 and eighty patients had a complete (CCR 0) or near complete (CCR 1) resection. At initial evaluation at our institution, the mean and median preoperative baseline platelet counts were 351,000/mm^3 and 305,000/mm^3,

TABLE 1 Clinicopathological factors of patients with MPM

	N	Percentage (%)
Sex		
Male	53	53
Female	47	47
Age (years)		
Mean	54	
Median	57	
Range	17–81	
Race		
White	85	85
Non-white	15	15
Previous chemotherapy		
Yes	29	29
No	71	71
Residual disease		
CCR $\leq$ 1	80	80
CCR $>$ 1	17	17
Unknown	3	3
Peritoneal cancer index		
$\leq$20	29	29
$>$20	65	65
Unknown	6	6
Platelet count		
Mean	351	
Median	305	
Range	109–1362	

respectively (range 109,000–1,362,000/mm^3). Ninety-seven patients for whom preoperative CBCs could be identified were dichotomized according to normal versus elevated platelet values as follows: $\leq$367,000/mm^3 ($n = 68$) and >367,000/mm^3 ($n = 29$), using the cutoff value at our institution for elevated platelet count, which is consistent with previous reports.[14,15]

A summary of the morbidity, mortality, and complications experienced in the patient cohort is shown in Table 2. Thirty-nine of 100 patients experienced at least one perioperative complication of which approximately half were grade 3 or 4 complications. Ten patients were returned to the operating room for reoperation. Perioperative mortality rate was 2% and average length of hospital stay was 11.4 days.

TABLE 2 Complications after operative cytoreduction and hyperthermic intraperitoneal chemotherapy in 100 patients with MPM

	N (%)
Patients with ≥1 complication	39/100 (40)
Patients returned to operating room	10/100 (10)
Operative mortality	2/100 (2)
Duration of hospital stay (days; median, range)	11.4 (0–75)
Types of complication (*n*)	
Cardiac complication	6
Respiratory complication	19
Gastrointestinal complication	20
Renal complication	3
Hematologic complication	2
Grade of morbidity (Clavien-Dindo)	
I–II	18/39
III–IV	21/39

Prognosis and Overall Survival of Patients with MPM After CRS and HIPEC

The median actuarial overall survival was 32.8 (range 0–103) months; the actuarial 1-, 3-, 5-years survivals were 70, 49, and 36%, respectively. Seven clinicopathological variables (sex, age, race, previous chemotherapy, CCR, PCI, and preoperative platelet count) were examined in 85 patients in whom complete data were available for potential association with overall survival. Univariate analysis identified five significant prognostic variables associated with improved overall survival: male sex ($P = 0.042$), no previous chemotherapy ($P = 0.006$), CCR $\leq$1 ($P < 0.001$), PCI $\leq$ 20 ($P < 0.001$), and normal preoperative platelet counts ($\leq$367,000/mm$^{3;}$ $P = 0.001$). Multivariate analysis of these five variables identified CCR > 1, PCI > 20, and elevated preoperative platelet count >367,000/mm^3 to be independently significant in predicting shortened overall survival after CRS and HIPEC (Table 3; Fig. 1). Median overall survival in patients with elevated versus normal pretreatment platelet counts were 13 versus 58 months, respectively ($P < 0.001$).

Relationship Between Preoperative Platelet Count and Clinicopathological Factors in Patients with MPM

The relationship between thrombocytosis and various clinicopathological variables were examined in 95 patients in whom we had complete data (platelet count, sex, age, race, previous chemotherapy, CCR, PCI; Table 4). Compared with patients with normal preoperative platelet counts ($\leq$367/mm^3), patients with elevated platelet counts had significantly more residual disease (CCR > 1) after

TABLE 3 Multivariate analysis of factors independently associated with outcome

	Hazard ratio	95% Confidence interval	Standard error	*P* value
Sex				
Male	1.62	0.85–3.07	0.33	0.14
Female	1			
Previous chemotherapy				
Yes	1.11	0.57–2.14	0.34	0.76
No	1			
Residual disease				
CCR > 1	2.70	1.32–5.51	0.36	<0.01
CCR ≤ 1	1			
PCI				
>20	2.81	1.10–7.22	0.48	0.03
≤20	1			
Platelet count				
Abnormal (>367)	2.42	1.30–4.49	0.32	<.01
Normal (≤367)	1			

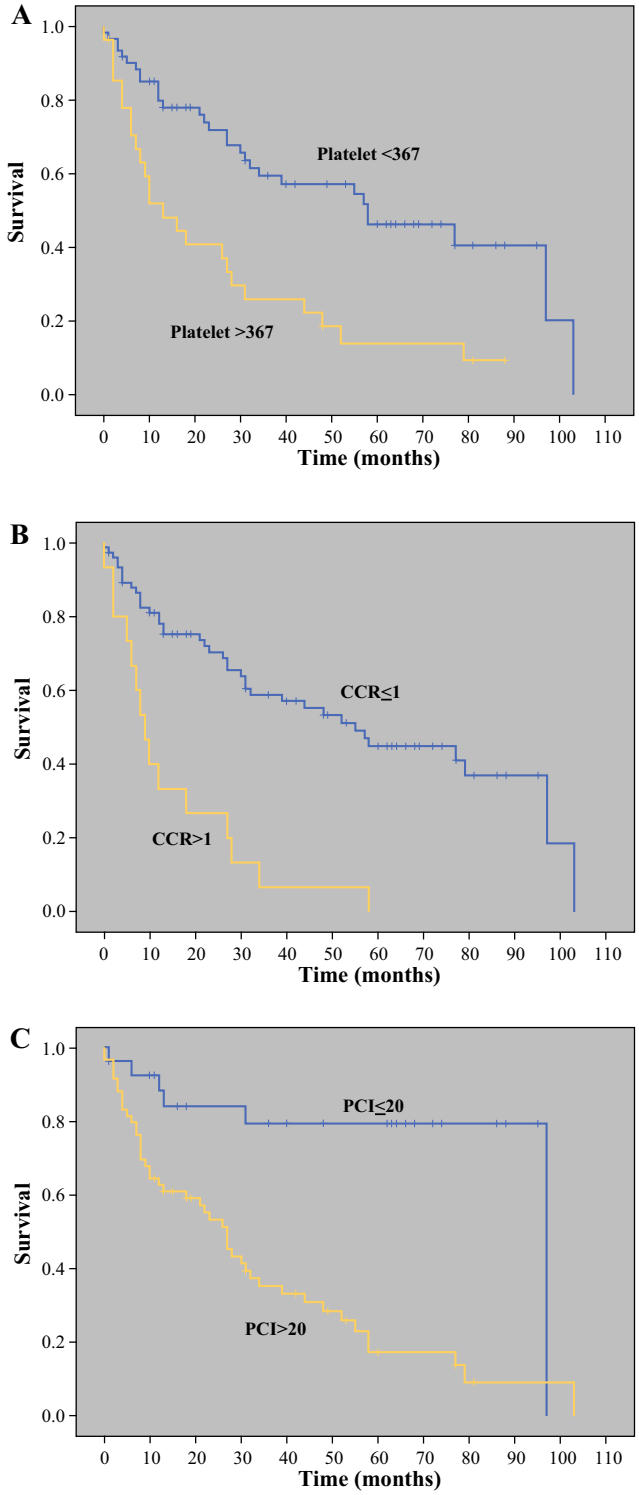

FIG. 1 Actuarial overall survival in patients with MPM was significantly shorter in patients with elevated preoperative platelet count (>367/mm^3) versus normal platelet count (≤367/mm^3) (**a**), patients who had suboptimal (CCR > 1) versus optimal cytoreduction (CCR ≤ 1) (**b**), and patients with high tumor burden indicated by PCI > 20 versus PCI ≤ 20 (**c**). All *P* values are <0.001

operation (Table 4). However, almost 90% of patients with baseline normal platelets (59/66) and two-thirds of patients with baseline thrombocytosis (18/27) had an optimal resection (CCR ≤ 1). In patients who had an optimal cytoreduction, median overall survival was still significantly shorter for those with preoperative thrombocytosis compared with patients with normal platelet counts, 27 and 77 months, respectively ($P = 0.02$). Aside from CCR, no other clinicopathological factor was found to be significantly associated with baseline platelet count (Table 4). Sixty-seven of 95 patients did not receive any form of chemotherapy before treatment, whereas 28 patients did receive chemotherapy previously, which was usually initiated prior to referral. However, there was no significant correlation between those previously treated with chemotherapy and thrombocytosis.

DISCUSSION

The data in this study represent a large, single-center experience showing that elevated preoperative platelet counts predicts shortened survival in patients with MPM undergoing CRS and HIPEC. Notably, thrombocytosis in this patient population appears to reflect aggressive tumor biology. Although tumor burden, as measured by PCI, was not significantly different between patients with or without baseline thrombocytosis, those with an elevated platelet count were more likely to undergo an incomplete tumor resection. However, it does not appear that incomplete resection alone can fully account for the differences in survival between the two groups. It was possible to achieve an optimal resection (CCR ≤ 1) in a majority of patients in both the normal and elevated platelet groups, 90 versus 66%, respectively. The fact that even after a therapeutic resection thrombocytosis still predicted shortened survival strongly suggests that disease in this group exhibited inherently more aggressive tumor biology compared with patients with normal platelet counts. The data in the current study indicate that patients with MPM and baseline thrombocytosis are not good candidates for immediate CRS and HIPEC. Although several studies have reported the prognostic significance of preoperative thrombocytosis for patients with various types of malignancies, this is the first study to demonstrate this relationship in MPM.

We believe these findings are generalizable as the data in this study indicate that our cohort is representative of those generally afflicted with this disease and who are considered good candidates for initial CRS and HIPEC. The patient demographics, tumor characteristics, treatment parameters, complication profile, and outcomes are consistent with previous reports.[7–9,11] We and others have

TABLE 4 Preoperative platelet count and clinicopathological factors

Variable	No. of patients	Platelet $\leq 367/mm^3$	Platelet $>367/mm^3$	*P* value
Sex				0.549
Male	52	38	14	
Female	43	29	14	
Age (years)				0.924
≤60	55	39	16	
>60	40	28	12	
Race				0.579
White	81	58	23	
Non-white	14	9	5	
Previous chemotherapy				0.712
Yes	28	19	9	
No	67	48	19	
Residual disease				0.008
CCR ≤ 1	77	59	18	
CCR > 1	16	7	9	
Peritoneal cancer index				0.294
≤20	28	22	6	
>20	62	42	20	

shown that various histologic features are associated with an aggressive tumor biology and poor survival, including high nuclear grade, high mitotic rate, extensive depth of invasion, presence of inflammatory infiltrate, and high Ki-67 immunostaining.[12,20,21] Kusamura and colleagues found that Ki-67 immunoexpression, a marker for cell proliferation, is a strong and independent factor associated with poor survival in patients with MPM; high Ki-67 in association with a high PCI was associated with a median survival of only 10 months.[21] We included only patients with high grade epithelioid mesothelioma in order to study a homogeneous cohort and our findings complement and extend the findings of previous reports. Interestingly, there was no relationship between thrombocytosis and PCI in our cohort, and even in those patients with thrombocytosis and a CCR ≤ 1, overall survival was still significantly shorter compared with those with normal platelet counts. These findings highlight the growing evidence that there are reliable surrogates for aggressive tumor biology that can be used in selecting patients for CRS and HIPEC.

What is provocative in the current study is that we have identified a systemic parameter, elevated platelet count, which is associated with poor outcome. The relatively small number of patients with thrombocytosis ($n = 29$) limits the value of an in depth analysis of this cohort, and we have not yet assessed the potential relationship between thrombocytosis and various histologic parameters. In addition we did not evaluate the prognostic significance of cancer antigen (CA) 125, because elevated CA 125 has not been consistently shown to be associated with poor survival in this patient population.[21,22] We believe CA 125 is best used as a biomarker for recurrence in patients who have elevated baseline levels.

The strong association between thrombocytosis and aggressive tumor biology may have therapeutic implications. Emerging evidence suggests that platelets have an active role in tumor progression through various mechanisms, including promoting tumor invasion and metastasis and regulating angiogenesis.[23–26] In vivo studies investigating thrombocytosis in mouse ovarian cancer models describe a paracrine circuit wherein tumor-derived interleukin (IL)-6 induces hepatic thrombopoietin synthesis, which stimulates thrombocytosis.[15] In the same study, Stone and colleagues implicated the active role of platelets in tumor growth, migration, and angiogenesis. Furthermore, our laboratory and others have shown that aggressive tumor behavior is strongly associated with IL-1 signaling and activation of the phosphoinostide inositol-3 kinase (PI3K) pathway.[10] IL-1 is known to induce IL-6 production, whereas PI3K signaling has been shown in experimental studies to be associated with inflammatory cytokine production and subsequently the inhibition of tumor apoptosis.[27,28] Recently, high levels of IL-6 have been measured in the ascitic fluid of patients with MPM, suggesting a strong role for this cytokine in the biological behavior of MPM.[29] We believe the interplay between tumor derived inflammatory cytokine production with secondary PI3K activation and thrombocytosis holds potential for therapeutic intervention and thus deserves additional study.

In summary, our data show that in a relatively large cohort of patients with MPM, preoperative elevated platelet count is a valuable parameter that can identify patients for whom CRS and HIPEC may not be appropriate as a first line therapeutic intervention. Although there is a strong association between incomplete cytoreduction and preoperative thrombocytosis, this alone is not sufficient to account for the differences in survival between the groups. Importantly, baseline thrombocytosis predicts an aggressive tumor biology for which platelets and other immunologic cytokines are revealed as potential targets of novel therapeutic interventions.

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