Preoperative Change in Peripheral Blood Monocyte Count May Predict Long-term Outcomes After Pancreaticoduodenectomy for Bile Duct Cancer

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Abstract. *Background/Aim: The perioperative immunological response predicts long-term outcomes after resection for malignant tumors. The aim of the study was to evaluate the significance of perioperative change in the peripheral blood monocyte count regarding therapeutic outcome after pancreaticoduodenectomy for bile duct cancer. Patients and Methods: The study comprised of 51 patients who had undergone pancreaticoduodenectomy for bile duct cancer between January 2000 and December 2012. We retrospectively investigated the relation between perioperative change in peripheral blood monocyte count and disease-free as well as overall survival. Results: In multivariate analysis, advanced TNM stage, and decrease in monocyte count on postoperative day 1 in comparison with those before surgery were independent and significant predictors of poor disease-free survival and overall survival (p=0.014 and 0.004, and 0.010 and 0.006, respectively). Conclusion: Perioperative change in peripheral blood monocyte count is an independent and significant indicator of therapeutic outcome after pancreaticoduodenectomy in patients with bile duct cancer.*

Bile duct cancer is an aggressive tumor with a poor outcome and is often diagnosed at an advanced stage (1). Pancreaticoduodenectomy with lymph node dissection is a potentially curative treatment for middle and distal bile duct cancer. Despite recent improvements in perioperative management and surgical techniques, the 5-year survival rate has been reported to range between 18% and 54% (1-7).

Therefore, assessment of prognostic indicators is important for postoperative management after surgical resection.

Recently, several studies have indicated that systemic inflammatory response predicts cancer-specific survival in patients with cancer. The Glasgow prognostic score (GPS), calculated by the combination of serum C-reactive protein (CRP) and albumin concentrations, and an elevated preoperative neutrophil-to-lymphocyte ratio (NLR) have been reported to predict cancer-specific survival (8-10). We reported the prognostic value of GPS for carcinoma of the ampulla of Vater (11) and gallbladder cancer (12), and the association between perioperative immunological response and prognosis after surgical resection for pancreatic (13) and gallbladder (14) cancer. Monocytes are known to play an important role in the acute phase of inflammation and in antitumor immunity. Therefore, in the present study, we retrospectively investigated the relation between perioperative change in peripheral blood monocyte count and disease-free as well as overall survival after pancreaticoduodenectomy in patients with bile duct cancer.

Patients and Methods

Between January 2000 and December 2012, 56 patients with bile duct cancer underwent pancreaticoduodenectomy at the Department of Surgery, Jikei University Hospital, Tokyo, Japan. Of these, five patients were excluded, two due to death from other diseases and three who were lost to follow up, leaving the remaining 51 patients for this study.

Hemogram and chemistry profile were routinely measured for each patient preoperatively and on postoperative day (POD) 1. Absolute white blood cell count, neutrophils, lymphocytes, monocytes, and each subset were routinely determined in peripheral venous samples. The changes in white blood cell count were determined as the ratio of the count on POD1 and that before surgery. Pathological stage was determined according to the fifth Japanese edition of the Japanese General Rules for Biliary Tract Cancer (15).

We first investigated the relation between clinicopathological variables and disease-free and overall survival after pancreaticoduodenectomy by univariate and multivariate analysis. The following 10 variables were evaluated: age, gender, presence of preoperative

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Key Words: Bile duct cancer, monocyte, immune supression, systemic inflammatory response.

Table I. *Patients' characteristics.*

Factor	Mean±SD or ratio	Range
Age (years)	68.0±7.6	43-82
Gender (male:female)	39:12	
Preoperative biliary drainage (present:absent)	44:7	
TNM stage (I:II:III:IV)	6:17:11:17	
Serum CA19-9 (U/ml)*	156.2±267.3	1-1,705
Duration of operation (min)	542.6±141.0	330-963
Intraoperative blood loss (g)	1,274.8±798.0	240-4,100
Change in neutrophil count (<3-fold:≥3-fold)	32:19	
Change in lymphocyte count (<50%:≥50%)	22:29	
Change in monocyte count (decrease:increase)	29:22	

TNM, Tumor node metastasis; CA19-9, carbohydrate antigen 19-9; *data missing in 4 cases.

biliary drainage, tumor-node-metastasis (TNM) stage based on pathology, serum carbohydrate antigen 19-9 (CA19-9), duration of operation, intraoperative blood loss, and change in neutrophil, lymphocyte, and monocyte count. Continuous clinicopathological variables were classified into two groups for the log-rank test and the Cox proportional hazard regression model as follows: age <65 and ≥65 years, CA19-9 <150 and ≥150 U/ml, duration of operation <540 and ≥540 minutes, and intraoperative blood loss <1,000 and ≥1,000 g. The mean or median of changes in white cell subsets counts were classified as follows: neutrophil count <3-fold or ≥3-fold, lymphocyte count <50% or ≥50%, and monocyte count decrease or increase.

Next, for the assessment of perioperative change in peripheral blood monocyte count, the patients were classified into two groups: decrease in monocyte count on POD 1 in comparison with that before operation, and increase in monocyte count on POD 1 in comparison with that before operation. We then investigated the relationship between clinicopathological variables and change in monocyte count by univariate analysis of the same variables as above.

Recurrence of bile duct cancer was defined as newly detected local or distant metastatic tumors by ultrasonoghapy, computed tomography, or magnetic resonance image with or without increase in serum CEA or CA 19-9.

This retrospective study was approved by the Ethics Committee of The Jikei University School of Medicine.

Statistical analysis. Data are expressed as the mean±standard deviation (SD). Univariate analysis was performed using the Mann–Whitney *U*-test and Chi-square test. Analysis of disease-free and overall survival was performed using the log-rank test. Multivariate analysis was performed using the Cox proportional regression model incorporating all variables with $p<0.05$ on univariate analysis. All *p*-values were considered statistically significant when the associated probability was less than 0.05. These analyses were conducted using IBM® SPSS statistics version 20.0 (IBM Japan, Tokyo, Japan).

Results

Patient characteristics. Patient characteristics are outlined in Table I as the mean±SD, range, or ratio. Twenty-nine out of 51 patients (56.9%) had a decrease in their perioperative monocyte count.

Univariate and multivariate analyses of clinicopathological variables in relation to disease-free survival after pancreaticoduodenectomy for bile duct cancer. Table II lists the relationship between the clinical variables and disease-free survival after pancreaticoduodenectomy for bile duct cancer. In univariate analysis, disease-free survival was significantly worse in patients with preoperative biliary drainage ($p=0.047$), advanced TNM stage ($p=0.002$), and decrease in monocyte count on POD1 in comparison with that before surgery ($p=0.007$; Figure 1A). In multivariate analysis, advanced TNM stage ($p=0.014$), and decrease in monocyte count on POD1 in comparison with that before surgery ($p=0.004$) were independent and significant predictors of poorer disease-free survival.

Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after pancreatico-duodenectomy for bile duct cancer. Table III lists the relationship between the clinical variables and overall survival after pancreaticoduodenectomy for bile duct cancer. In univariate analysis, overall survival was significantly worse in patients with preoperative biliary drainage ($p=0.037$), advanced TNM stage ($p<0.001$), and decrease in monocyte count on POD1 in comparison with that before surgery ($p=0.003$; Figure1B). In multivariate analysis, advanced TNM stage ($p=0.010$), and decrease in monocyte count on POD1 in comparison with that before surgery ($p=0.006$) were independent and significant predictors of poorer overall survival.

Association between clinicopathological variables and change in monocyte count. Table IV lists the relationship between clinicopathological variables and perioperative changes in monocyte count. In univariate analysis, change in neutrophil count was positively correlated with perioperative change in monocyte count ($p=0.041$).

Discussion

Several perioperative findings have been reported to correlate with outcome after operation in patients with bile duct cancer, including lymph node metastases (2-4), resection margin status (4), tumor differentiation (2, 5), depth of invasion (6) and adjuvant chemotherapy (7). In the present study, perioperative change in monocyte count and advanced TNM stage were independent and significant

Table II. *Univariate and multivariate analyses of clinicopathological variables in relation to disease-free survival after pancreaticoduodenectomy for bile duct cancer.*

Factor	N	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Age (years)					
≥65	33	1.211 (0.5551-2.644)	0.541		
<65	18	1.0			
Gender					
Male	39	0.6463 (0.2472-1.690)	0.448		
Female	12	1.0			
Preoperative biliary drainage					
Yes	44	2.649 (0.9914-7.078)	0.047	3.170 (0.390-25.765)	0.280
No	7	1.0		1.0	
TNM stage					
III or IV	30	3.144 (1.464-6.752)	0.002	3.154 (1.261-7.889)	0.014
II or I	21	1.0		1.0	
Serum CA19-9 (U/ml)*					
≥150	14	2.505 (0.1023-6.132)	0.067		
<150	33	1.0			
Duration of operation (min)					
≥540	24	1.772 (0.8297-3.785)	0.203		
<540	27	1.0			
Intraoperative blood loss (g)					
≥1,000	27	1.087 (0.5082-2.323)	0.993		
<1,000	24	1.0			
Change in neutrophil count					
<3-Fold	32	0.8907 (0.3870-2.050)	0.598		
≥3-Fold	19	1.0			
Change in lymphocyte count					
<50%	22	1.080 (0.4984-2.340)	0.681		
≥50%	29	1.0			
Change in monocyte count					
Decrease	29	2.747 (1.271-5.936)	0.007	3.360 (1.457-7.745)	0.004
Increase	22	1.0		1.0	

TNM, Tumor node metastasis; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; *data missing in 4 cases.

prognostic factors of patients with bile duct cancer after pancreaticoduodenectomy.

Antitumor immunity plays an important role in tumor progression and prognosis. The presence of tumor-infiltrating CD8^{+} lymphocytes have been reported as predictor of survival in patients with bile duct cancer (16). Antitumor immune response also is associated with systemic inflammatory response. Indeed, monocytes are the main regulators of cancer-related inflammation, and have an essential role in the systemic inflammatory response. The lymphocyte to monocyte ratio, which might be a good reflection of weak immune response and the tumor microenvironment, has been reported as a prognostic factor in colon (17) and pancreatic (13) cancer.

Major gastrointestinal surgery, such as pancreaticoduo-denectomy, has been reported to cause stress-induced immunosuppression. After pancreaticoduodenectomy, T-helper 1 cells secrete interferon-gamma and interleukin-2, which induce a cell-mediated immune response, including activation of macrophages and monocytes. An increase in interferon-gamma and interleukin-2 from T-helper 1 cells is associated with reduced immune suppression (18). Therefore, the attenuation of increase or decrease in perioperative monocyte counts implies an immunosuppressive state due to response to surgical stress. In patients with malignant tumors, the immunosuppressive state is associated with tumor progression and metastasis formation because of decreased activity of natural killer cells and increased activity of regulatory T-cells (19, 20). For liver resection, the perioperative change in monocyte count has also been reported to predict survival in patients with liver metastases from colorectal cancer (21).

Table III. *Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after pancreaticoduodenectomy for bile duct cancer.*

Factor	N	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Age (years)					
≥65	33	1.391 (0.6227-3.108)	0.426		
<65	18	1.0			
Gender					
Male	39	0.5731 (0.2109-1.557)	0.277		
Female	12	1.0			
Preoperative biliary drainage					
Present	44	3.275 (1.070-10.02)	0.037	2.935 (0.363-23.755)	0.313
Absent	7	1.0		1.0	
TNM stage					
III or IV	30	4.185 (1.901-9.217)	<0.001	4.922 (1.464-16.545)	0.010
II or I	21	1.0		1.0	
Serum CA19-9 (U/ml)*					
≥150	14	2.422 (0.9877-5.938)	0.054		
<150	33	1.0			
Duration of operation (min)					
≥540	24	1.404 (0.6362-3.100)	0.404		
<540	27	1.0			
Intraoperative blood loss (g)					
≥1,000	27	1.427 (0.6494-3.137)	0.379		
<1,000	24	1.0			
Change in neutrophil count					
<3-Fold	32	0.7211 (0.3067-1.696)	0.457		
≥3-Fold	19	1.0			
Change in lymphocyte count					
<50%	22	1.431 (0.6379-3.210)	0.388		
≥50%	29	1.0			
Change in monocyte count					
Decrease	29	3.555 (1.562-8.094)	0.003	3.701 (1.455-9.412)	0.006
Increase	22	1.0		1.0	

TNM, Tumor node metastasis; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; *data missing in 4 cases.

Table IV. Univariate analysis of clinicopathological variables in relation to change in monocyte count.

Factor	Change in monocyte count		*p*-Value
	Decrease (n=29)	Increase (n=22)	
Age (years)	69.6±6.5	66.0±8.5	0.145
Gender (male:female)	21:8	18:4	0.518
Preoperative biliary drainage (present:absent)	25:4	19:3	1.000
TNM stage (I:II:III:IV)	3:9:5:12	3:6:6:7	0.785
Serum CA19-9 (U/ml)	198.4±347.1	104.1±92.4	0.923
Duration of operation (min)	536.6±133.2	550.6±153.5	0.872
Intraoperative blood loss (g)	1,285.4±906.3	1,260.8±648.7	0.536
Change in neutrophil count (<3-fold:≥3-fold)	22:7	10:12	0.041
Change in lymphocyte count (<50%:≥50%)	15:14	7:15	0.253

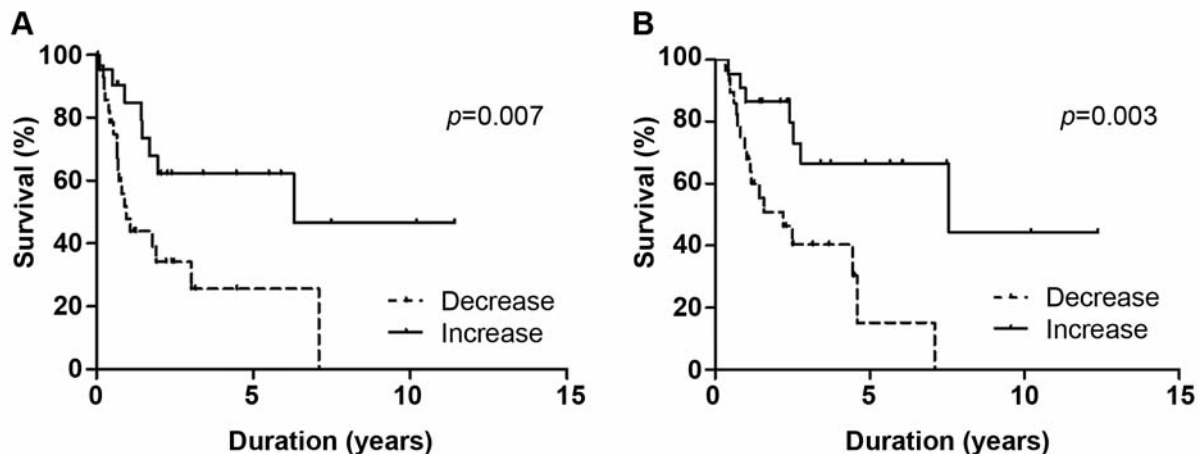TNM, Tumor node metastasis; CA19-9, carbohydrate antigen 19-9.

Figure 1. *Kaplan–Meier curves of disease-free (A) and overall survival (B) after pancreaticoduodenectomy for bile duct cancer according to change in monocyte count. A decrease in monocyte count on postoperative day 1 in comparison with that before surgery was significantly associated with worse disease-free (p=0.007) and overall (p=0.003) survival.*

Systemic inflammation has been reported to correlate with poor cancer-specific survival in various types of cancer (8-12). The host's inflammatory response to cancer and the systemic effects exerted by the cancer cells lead to up-regulation of the inflammatory process. This condition may accelerate with the proliferation and metastasis of cancer (22, 23). The presence of a systemic inflammatory response can be detected by elevation of the CRP level and the neutrophil count. In this study, patients with a decrease in monocyte count had a higher preoperative CRP level (*p*=0.043, data not shown) compared with patients with an increase in monocyte count. These results seem to suggest that preoperative systemic inflammation leads to suppression of the immune response after surgery.

Prevention of immunosuppression may improve long-term outcomes after surgical treatment. Several immune-enhancing treatments reduced perioperative immunosuppression, including perioperative immunonutrition (18, 24). Further investigation to clarify the relationship between immunosuppressive mechanisms and tumor progression is important to improve the therapeutic outcome of oncological surgery. In conclusion, perioperative change in peripheral blood monocyte count was a predictor of the outcome in patients with bile duct cancer in both disease-free and overall survival after pancreaticoduodenectomy.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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