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Elevated neutrophil to lymphocyte ratio predicts survival in advanced pancreatic cancer

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Abstract

Background: Elevated neutrophil to lymphocyte ratio (NLR) is linked with worse survival in many malignancies, whereas its association with pancreatic cancer (PC) remains unclear.

Methods: We retrospectively reviewed 95 patients with locally advanced or metastatic PC receiving gemcitabine-based chemotherapy. The prognostic value of NLR was evaluated.

Results: Elevated pretreatment NLR (>5) was observed in 16 out of 89 eligible patients, which was identified as an independent prognostic factor for overall survival (OS). The median OS for patients with elevated and normal NLR were 2.4 months and 7.7 months, respectively (p <0.001).

Conclusions: Elevated NLR is a predictor of shorter survival in patients with advanced PC.

Keywords: *Chemotherapy; gemcitabine; neutrophil to lymphocyte ratio (NLR); pancreatic cancer*

Introduction

Pancreatic cancer (PC) is one of the most malignant diseases in the world with extremely poor prognosis. At the time of diagnosis, most patients present locally advanced (40%) or metastatic (40–45%) disease, and have a median survival of 8–12 months or 3–6 months, respectively (Nieto et al. 2008, de Braud et al. 2004). For unresectable patients, systemic chemotherapy is the standard therapy. The National Comprehensive Cancer Network (NCCN) recommends gemcitabine (GEM) monotherapy as the standard first-line chemotherapy, and GEM-based combination therapy as another choice for patients with good performance status (PS) in order to achieve a higher response rate. However, the response rate is no more than 40% (Herrmann et al. 2007, Heinemann et al. 2006, Baize et al. 2005), and the outcome of patients cannot be predicted before chemotherapy. Therefore, it is essential to identify specific pretreatment prognostic factors to determine subgroups of patients who would benefit from GEM-based chemotherapy. We previously reported that the serum CA19-9 level could predict survival of patients with advanced PC treated with GEM-based chemotherapy (An et al. 2009). However, not all PC patients show an elevated CA19-9 level. Moreover, dynamic monitoring post-chemotherapy CA19-9 change is required to provide more predictive information.

Recently, blood neutrophil to lymphocyte ratio (NLR), a marker of systemic inflammatory response, has been found to be an important prognostic factor for a number of malignancies, including colorectal cancer (Halazun et al. 2008, Kishi et al. 2009), non-small cell lung cancer (Sarraf et al. 2009), ovarian cancer (Cho et al. 2009), intrahepatic cholangiocarcinoma (Gomez et al. 2008b) and hepatocellular carcinoma (Gomez et al. 2008a). However, whether or not NLR is associated with the prognosis of PC patients is still unknown. To our knowledge, only one study (Engelken et al. 2003) has reported leukocytosis predicting shorter survival for unresectable PC patients, and two small sampled studies (Fogar et al. 2006, Clark

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et al. 2007) showed that lower lymphocyte count is an index of adverse outcome in patients with PC. However, no study has explored the impact of a combination of neutrophil and lymphocyte counts on the prognosis of patients with advanced PC. Therefore, we hypothesized that NLR, the marker that combines the information of both neutrophil and lymphocyte counts, could better predict the prognosis of PC patients.

The aim of this study was to assess the prognostic value of an elevated NLR in patients with advanced PC treated with GEM-based chemotherapy.

Patients and methods

Study subjects

We retrospectively reviewed 95 patients with unresectable locally advanced or metastatic PC from March 2001 to June 2008 in the Cancer Center of Sun-Yat Sen University. All patients met the following criteria: (1) pathologically proven PC; (2) chemotherapy-naive and receiving first-line GEM-based chemotherapy; (3) World Health Organization (WHO) performance status (PS) 0–2; (4) signed informed consent forms. Demographic, clinical, histopathological and laboratory data, including patients' age, sex, tumour location, histological grade, white blood cell (WBC) and differential counts, tumour marker (CA19-9) level, and presenting features were recorded. WBC with differential was measured using a Beckman Coulter STKS/MaxM/5 diff (Beckman Coulter Inc., Fullerton, CA, USA). Serum CA19-9 level was measured by a commercially available enzyme immunoassay (electrochemiluminescence immunoassay, Elecsys 1010; Roche Diagnostics GmbH, Mannheim, Germany).

All eligible patients received GEM monotherapy (1000 mg m^{-2} weekly for 7 weeks, followed by a break of 1 week, and subsequently for 3 weeks out of every 4 weeks) or received one of the following GEM-based combination chemotherapy regimens: GEM (1000 mg m^{-2} on days 1 and 8 of a 21-day cycle) plus oxaliplatin (130 mg m^{-2} on day 1), or 5-fluorouracil (5-Fu)/leucovorin (LV) (bolus 5-Fu 425 mg m^{-2} plus LV 20 mg m^{-2}, days 1–5 of a 21-day cycle), or capecitabine (1000 mg m^{-2} twice a day PO on days 1–14 of a 21-day cycle), or cisplatin (40 mg m^{-2} on days 1 and 8 of a 21-day cycle).

Computed tomography (CT) scan or magnetic resonance imaging (MRI) was performed before treatment and thereafter every two cycles of chemotherapy. The Response Evaluation Criteria in Solid Tumors (RECIST) was applied for evaluation (Therasse et al. 2000). Clinical benefit was evaluated according to Andersen and Rothenberg's definition (Rothenberg et al. 1996). Overall survival (OS) was defined as the time from starting chemotherapy to death or last follow-up.

Complete blood count with differential

All WBC and differential counts were examined on the day before chemotherapy, and none of the patients had clinical symptoms or signs of sepsis. The normal range for total WBC count in our hospital is $4–10 \times 10^9$ l^{-1}. The normal percentage range of neutrophils and lymphocytes is 50–70% and 20–40%, respectively. The NLR was calculated from the differential count by dividing the absolute neutrophil count by the absolute lymphocyte count. NLR >5 was considered elevated in accordance with the published literature (Halazun et al. 2008, Kishi et al. 2009, Gomez et al. 2008a).

Statistical analysis

Statistical analysis was performed using the statistical package SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL, USA). Survival curves were made using the Kaplan–Meier method and compared by the log-rank test. Univariate and multivariate analyses to identify prognostic predictors were performed by Cox proportional hazard regression models. A p-value of less than 0.05 was considered statistically significant.

Results

Demographic data

Ninety-five patients met the eligible criteria, among whom six patients were excluded for failing to attend follow-up. The remaining 89 patients were further analysed. The median age was 55 years (range 29–79). Fifty-nine (66.3%) patients were male and 30 (33.7%) were female. Seventy patients (78.7%) had a PS of 0–1, and 19 patients (21.3%) had a PS of 2. The primary tumours were located in the head of pancreas in 59 cases (66.3%), and in the body or tail of the pancreas in 30 cases (33.7%). Seventy patients (78.7%) had metastatic disease and 19 patients (21.3%) had locally advanced disease. The most common metastatic site was liver (56 cases, 62.9%), followed by peritoneum (23 cases, 25.8 %) and lungs (nine cases, 10.1%). Prior to chemotherapy, ten patients (11.2%) with obstructive jaundice underwent endoscopic biliary prosthesis, and total serum bilirubin levels of all patients returned to the normal range before chemotherapy. Eleven patients (12.4%) had palliative operations and five patients (5.6%) had recurrent metastatic disease after previous Whipple's pancreatoduodenectomy. Most patients had moderately (17, 19.1%) or poorly differentiated (48, 53.9%) adenocarcinoma. Fifteen patients (16.9%) had normal baseline CA19-9 values and 74 patients (83.1%) had elevated CA19-9 values with the median baseline CA19-9 concentration of 662 U l^{-1} (range 44–100 000 U l^{-1}). Seventeen patients (19.1%) received GEM monotherapy and 72 patients (80.9%) received GEM

combination chemotherapy. The median accumulated dosage for GEM was 8.3 (2–19) g m^{-2}. Seven out of 19 patients (36.8%) with locally advanced disease received palliative radiotherapy. The baseline characteristics of all the 89 patients are presented in Table 1.

Treatment outcomes

All the patients were followed until death. The median OS for all the patients was 6.6 months (range 0.6–41 months), and the 3-month, 6-month, 1-year and 2-year OS rates were 77.5%, 56.2%, 18.0% and 4.5%, respectively. Objective partial response rate was achieved in 25 patients (28%). Clinical benefit response (CBR) rate was achieved in 34 patients (38%).

Table 1. Patient characteristics.

Characteristic	
Age (years), median (range)	55 (29–79)
NLR, median (range)	2.62 (0.7–29.75)
WBC count (x 10^9), median (range)	9.77 (3.60–15.3)
Neutrophil count (x 10^9), median (range)	5.26 (1.90–13.1)
Lymphocyte count (x 10^9), median (range)	1.71 (0.4–4.9)
Gender	
M	59 (66.3)
F	30 (33.7)
PS	
0	2 (2.2)
1	68 (76.4)
2	19 (21.3)
Primary tumour site	
Head	59 (66.3)
Body and tail	30 (33.7)
Tumour stage	
Locally advanced (stage III)	19 (21.3)
Metastatic (stage IV)	70 (78.7)
Tumour grade	
Well differentiated	10 (11.2)
Moderately differentiated	17 (19.1)
Poorly differentiated	48 (53.9)
Not documented	14 (15.7)
Previous operation	
Whipple's pancreatoduodenectomy	5 (5.6)
Exploration	4 (4.5)
Bypass	7 (7.9)
Stent	10 (11.2)
No	63 (70.8)
Chemotherapy	
GEM	17 (19.1)
GEM+OXA	39 (43.8)
GEM+5-Fu/CF	24 (27.0)
GEM+ Cap	5 (5.6)
GEM+ DDP	4 (4.5)
CA19-9	
Normal (≤35 U ml^{-1})	15 (16.9)
Elevated (>35 U ml^{-1})	74 (83.1)

Data are presented as number of patients (%) unless otherwise indicated.

NLR, neutrophil to lymphocyte ratio; WBC, white blood cell; PS, performance status; GEM, gemcitabine; OXA, oxaliplatin; 5-FU, 5-fluorouracil; CF, leucovorin; Cap, capecitabine; DDP, cisplatin; CA19-9, carbohydrate antigen 19-9.

Impact of lymphocyte, neutrophil and NLR on survival of advanced PC

We analysed the neutrophil and lymphocyte counts of all the 89 patients. The results were as follows: 23 patients had both increased neutrophil and decreased lymphocyte counts, three patients had an increased neutrophil count without a decreased lymphocyte count, six patients had a decreased lymphocyte count without an increased neutrophil count, and 57 patients had neither increased neutrophil nor decreased lymphocyte counts. Kaplan–Meier survival analysis showed that the median OS in patients with both increased neutrophil and decreased lymphocyte counts was 2.7 months, compared with 4.7 months in patients with either an increased neutrophil count and a non-decreased lymphocyte, or decreased lymphocyte count and a non-increased neutrophil ($p = 0.049$) count, and 8.6 months for patients with neither increased neutrophil nor decreased lymphocyte counts ($p < 0.001$) (Figure 1).

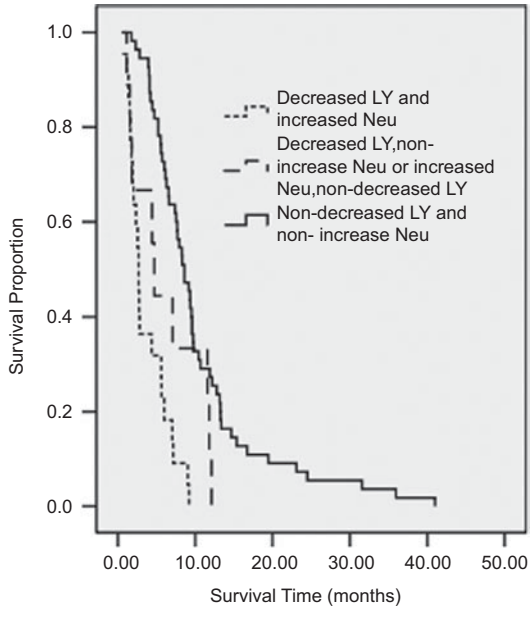

Figure 1. Overall survival of all 89 patients according to different neutrophil and lymphocyte counts before chemotherapy. The Kaplan–Meier survival curves show that median overall survival in patients with both increased neutrophil and decreased lymphocyte counts (23 patients) was 2.7 months, compared with 4.7 months in patients with either increased neutrophil, non-decreased lymphocyte (three patients) or decreased lymphocyte, non-increased neutrophil counts (six patients) ($p = 0.049$), and 8.6 months for patients with neither increased neutrophil nor decreased lymphocyte counts (57 patients) ($p < 0.001$). Neu, neutrophil; Ly, lymphocyte.

Sixteen out of 89 patients (18%) had an elevated NLR (>5) before chemotherapy. All the 16 patients had both increased neutrophil and decreased lymphocyte counts. The median OS for these 16 patients was 2.4 months, compared with 6.0 months for the remaining seven patients with both increased neutrophil and decreased lymphocyte counts but an NLR <5 ($p = 0.050$) (Figure 2).

Analysis of predictors of survival

Potential risk factors for death are shown in Table 2. By univariate analysis, a PS of 2, pancreatic head tumour, metastatic disease (stage IV), poorly differentiated disease, increased total WBC count, increased neutrophil, decreased lymphocyte, elevated NLR (>5) and elevated prechemotherapy CA19-9 level (> median 662 U l^{-1}) were associated with a shorter survival time. However, only the NLR and the baseline serum CA19-9 level remained significant on subsequent multivariate analysis.

Further survival analysis showed a significant difference in OS between patients with normal and elevated pretreatment NLR levels, as shown in Figure 3. The median OS for patients with an elevated NLR was 2.4 months compared with 7.7 months for patients with a normal NLR (p <0.001), and 1-year OS rates were 0% and 22.5%, respectively. Baseline CA19-9 was another independent prognostic factor for OS. The median OS for patients with a baseline CA19-9 above the median value (662 U ml^{-1}) was 5.2 months compared with 8.3 months for those with a CA19-9 level below the median level ($p = 0.009$), and 1-year OS rates were 11.5% and 30.8%, respectively (Figure 4).

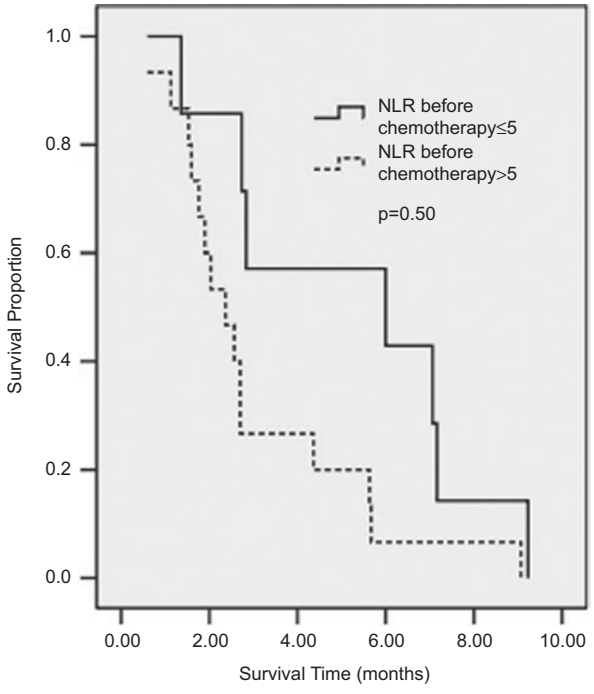

Figure 2. Stratifying the survival of patients with both increased neutrophil and decreased lymphocyte counts by neutrophil to lymphocyte ratio (NLR). The Kaplan–Meier survival curves show that median overall survival was 2.4 months in 16 patients whose prechemotherapy NLR was >5 compared with 6.0 months for the remaining seven patients with both increased neutrophil and decreased lymphocyte counts but an NLR ≤5 ($p = 0.050$).

Discussion

The NLR, an inexpensive, reproducible and widely available blood test, has been found to be an important prognostic predictor for a number of malignancies, including colorectal cancer (Halazun et al. 2008, Kishi et al. 2009), non-small cell lung cancer (Sarraf et al. 2009), ovarian cancer (Cho et al. 2009), intrahepatic cholangiocarcinoma (Gomez et al. 2008b) and hepatocellular carcinoma (Gomez et al. 2008a). Although the association between an elevated NLR and an adverse outcome in patients with PC has never been elucidated, several small studies have implied their potential association. Engelken et al. (2003) found leukocytosis (WBC $>11 \times 10^9$ l^{-1}) was an independent predictor of short survival for unresectable PC patients treated with palliative interventions. Fogar et al. (2006) found that total lymphocyte counts in blood were lower in PC patients than in those with benign pancreatic disease. Also, lymphocytes were lower in advanced PC stages (IIB–IV) compared with early stages (0–IIA). Moreover, the number of circulating lymphocytes could negatively predict survival of PC patients independent of tumour stage. Clark et al. (2007) reported that the preoperative lymphocyte count was a significant prognostic factor in resected pancreatic ductal adenocarcinoma. The median survival time for patients with a lymphocyte count above and below 1.5×10^9 l^{-1} was 14.3 months and 8.8 months, respectively. Ong et al. (2008) reported that an elevated NLR level was a predictive marker of unresectability for patients with potentially resectable pancreatic adenocarcinoma.

The present study assessed the prognostic value of pretreatment neutrophil count, lymphocyte count and NRL for patients with advanced PC receiving GEM-based chemotherapy. The results showed that patients with both increased neutrophil and decreased lymphocyte counts had the worst OS compared with patients with either increased neutrophil counts, non-decreased lymphocyte or decreased lymphocyte counts, non-increased neutrophil counts and patients with neither increased neutrophil nor decreased lymphocyte counts, suggesting that the combination of neutrophil and lymphocyte counts could provide more prognosis information than either component alone. Moreover, among the 23 patients with both increased neutrophil and decreased lymphocyte counts, the median OS for patients with an elevated NLR was significantly shorter than for patients with a normal

Table 2. Univariate and multivariate analysis of variables correlated to overall survival.

		Univariate analysis		Multivariate analysis	
	Median OS (months)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)
Age					
≤ 60 years (*n* = 58)	7.7				
>60 years (*n* = 31)	5.7	0.198	1.34 (0.86–2.08)		
Gender					
M (*n* = 59)	6.5				
F (*n* = 30)	7.7	0.472	0.85 (0.55–1.33)		
PS					
0–1 (*n* = 70)	7.7				
2 (*n* = 19)	3.7	0.016	2.32 (1.33–4.05)	0.512	1.371 (0.535–3.513)
Tumour location					
Head (*n* = 59)	5.6				
Body and tail (*n* = 30)	9.0	0.006	0.521 (0.327–0.832)	0.829	0.836 (0.163–4.272)
Stage					
Locally advance	9.3				
Metastasis	6.0	0.041	0.629 (0.373–0.829)	0.577	0.758 (0.285–2.012)
Grade					
Well differentiated	9.6				
Moderately differentiated	7.2				
Poorly differentiated	5.7				
Not documented	6.0	0.016	1.399 (1.065–1.837)	0.267	1.242 (0.847–1.822)
Liver metastasis					
Absent	7.7				
Present	6.0	0.436	1.264 (0.700–2.283)		
Jaundice					
Absent	7.2				
Present	5.5	0.302	1.399 (0.737–2.657)		
Total WBC (x 10^9 l^{-1})					
≤10	7.7				
>10	2.0	0.001	2.416 (1.443–4.408)	0.455	1.469 (0.536–4.028)
Increased neutrophil count					
Yes	2.7				
No	8.6	<0.001	4.871 (2.855–8.310)	0.057	2.637 (0.971–7.165)
Decreased lymphocyte count					
Yes	2.7				
No	8.3	<0.001	0.327 (0.203–0.527)	0.061	0.443 (0.188–1.040)
NLR					
≤5	7.7				
>5	2.4	<0.001	5.769 (3.133–10.622)	0.013	4.489 (1.372–14.692)
Hb (g l^{-1})					
≤110	7.7				
>110	8.5	0.904	1.032 (0.619–1.721)		
Platelets (x 10^9 l^{-1})					
≤300	8.3				
>300	6.6	0.117	1.516 (0.897–2.562)		
LDH					
≤245 IU l^{-1}	8.6				
>245 IU l^{-1}	7.0	0.173	0.504 (0.367–1.251)		
CA19–9 (median)					
Above median	5.2				
Below median	8.3	0.009	2.212 (1.224–3.998)	0.010	2.95 (1.289–6.753)

OS, overall survival; HR, hazard ratio; CI, confidence interval; PS, performance status; WBC, white blood cell; Hb, haemoglobin; LDH, lactate dehydrogenase; CA19-9, carbohydrate antigen 19-9; NLR, neutrophil to lymphocyte ratio.

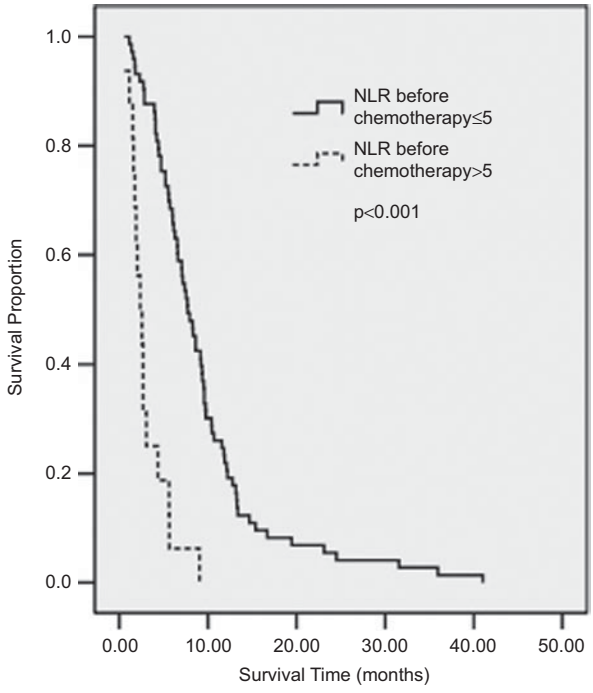

Figure 3. Overall survival of all 89 patients according to neutrophil to lymphocyte ratio (NLR) before chemotherapy. The Kaplan–Meier survival curves show that patients with a prechemotherapy NLR >5 (16 patients) had significantly worse overall survival than those with an NLR ≤5 (73 patients) (2.4 months vs 7.7 months, p <0.001).

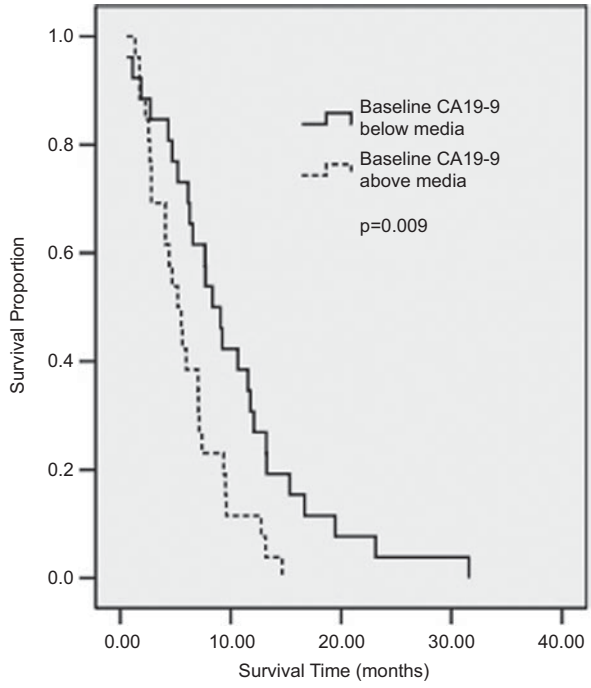

Figure 4. Overall survival of 74 patients with elevated carbohydrate antigen 19-9 (CA19-9) level according to baseline CA19-9 concentration. The Kaplan–Meier survival curves show that patients with a baseline CA19-9 concentration above the median value had significantly shorter median survival than patients with baseline concentrations below the median value (5.2 months vs 8.3 months; p = 0.009). NLR, neutrophil to lymphocyte ratio.

NLR, suggesting that the NLR could further identify subgroups of patients with a poorer prognosis among patients with both increased neutrophil and decreased lymphocyte counts. Subsequent univariate and multivariate analyses confirmed the better prognostic value of prechemotherapy NLR than either neutrophil or lymphocyte counts. Although increased WBC and neutrophil, and decreased lymphocyte counts were all significantly associated with the risk of death in the univariate analysis, none showed significance in the multivariate analysis, whereas the NLR was discovered to be a more powerful predictor of death than either component alone. Patients with an elevated pretreatment NLR had a significantly worse median survival than those with a normal NLR. To our knowledge, this is the first study to establish the relationship between an elevated pretreatment NLR value and poor prognosis in patients with advanced PC. As all patients in our study were treated with GEM-based chemotherapy, we were able to minimize potential bias related to differential treatment modality.

Until now, the association between an elevated NLR and poor prognosis has not been fully understood, while most studies (including the present study) suggest that both a neutrophil-dependent inflammatory reaction and a lymphocyte-mediated immune response contribute to the poor prognosis. Elevated neutrophil counts may aid in the development and progression of the neoplasm by providing an adequate environment for tumour growth. Circulating neutrophils have been shown to produce a vast majority of the inflammatory cytokines and chemokines, such as tumour necrosis factor, interleukin (IL)-1 and IL-6, which contributes to a progression of malignancy (Balkwill & Mantovani 2001). Neutrophils also secrete vascular endothelial growth factor (VEGF), a proangiogenic factor that is involved in tumour development (Kusumanto et al. 2003). Meanwhile, patients with elevated NLR usually have a relative lymphocytopenia, resulting in a suboptimal lymphocyte-mediated immune response to malignancy. Fogar et al. (2006) found that CD8+ suppressor T lymphocytes were higher and CD4+ T-helper lymphocytes were lower in PC patients compared with normal control and chronic pancreatitis patients, suggesting that a disturbance of the lymphocyte-mediated immune response may also contribute to the poor prognosis of PC.

A number of other clinicopathological factors were also analysed in this study. The results showed that the prechemotherapy serum CA19-9 level was another independent prognostic marker for patients with advanced PC. The median OS was significantly shorter in patients with a baseline CA19-9 concentration above the median value (662 U ml^{-1}) than in patients with baseline CA19-9 concentrations below the median value. The result is consistent with other reports and our previous studies (Maisey et al. 2005, Hess et al. 2008, An et al. 2009).

In summary, an elevated NLR (>5) is a useful predictor of worse survival in patients with advanced PC treated with GEM-based chemotherapy. Preoperative NLR measurement may therefore provide a simple method of identifying patients with a poor prognosis.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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