Original Article

Significance of Baseline and Changes of Tumor Markers and Neutrophil-to-Lymphocyte Ratio in Predicting Overall Survival for Patients with Advanced Pancreatic Adenocarcinoma: A Retrospective Analysis

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Abstract

Background: The usefulness of various prognostic factors for pancreatic cancer has been reported, but limited studies have focused on these changes during chemotherapy. The purpose of the present study was to investigate the prognostic factors and to evaluate the significance of these changes during chemotherapy in patients with advanced pancreatic cancer (APC). **Materials and Methods:** We retrospectively analyzed 213 patients with APC who underwent chemotherapy between January 2006 and December 2018 at Kofu Municipal Hospital and University of Yamanashi Hospital. Univariate and multivariate cox regression models were applied to investigate independent prognostic factors. **Results:** Multivariate analysis revealed that Eastern Cooperative Oncology Group Performance Status 2 (hazard ratio [HR] 4.07, $P < 0.01$), neutrophil-to-lymphocyte ratio (NLR) ≥3.9 (HR 1.97, $P < 0.001$), modified Glasgow prognostic score 1–2 (HR 2.77, $P < 0.001$), carcinoembryonic antigen ≥5.0 (HR 1.44, $P = 0.026$), carbohydrate antigen 19-9 ≥37 (HR 1.83, $P = 0.004$), ΔNLR >0 (HR 2.01, $P < 0.001$), ΔCEA (subtracting the baseline from the start of second cycles of chemotherapy) >0 (HR 1.64, $P = 0.002$), and ΔCA19-9>0 (HR 1.77, $P = 0.002$) were independent negative prognostic factors. **Conclusion:** Baseline and change in tumor markers and NLR are useful in predicting overall survival in APC patients undergoing chemotherapy.

Keywords: Carbohydrate antigen 19-9, carcinoembryonic antigen, chemotherapy, neutrophil-to-lymphocyte ratio, pancreatic cancer, prognostic factor

INTRODUCTION

Pancreatic cancer remains to be the deadliest malignancy among common tumors and the seventh leading cause of cancer-related

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death worldwide.[1] Approximately 45,750 patients in the United States would die of this disease in 2019.[2] In Japan, over 40,000 patients are diagnosed annually, with the majority of patients dying as a result of the disease, culminating in an estimated 35,000 deaths.[3] The mortality rates closely follow incidence rates because of poor overall survival (OS).

Palliative chemotherapy has been shown to prolong survival in patients with advanced pancreatic cancer (APC), but their OS is generally very poor. Therefore, it is important to identify prognostic factors and predict patient survival to help clinicians implement better therapeutic strategies. Several clinical and laboratory factors have been identified as independent prognostic factors in patients with APC, such as Eastern Cooperative Oncology Group (ECOG) Performance Status (PS),[4-8] carcinoembryonic antigen (CEA),[9,10] carbohydrate antigen 19-9 (CA19-9),[6,11-15] neutrophil-to-lymphocyte ratio (NLR),[4,8,16,17] and modified Glasgow prognostic score (mGPS).[4,8,18]

A decline in CA19-9 level from baseline to the time of response evaluation is considered prognostic.[5,19-23] Neutrophil and lymphocyte count may be influenced by a host of clinical factors such as medical treatments, coexisting infection, and impaired renal or hepatic function. Chemotherapy could have a significant impact on patients' inflammation environment. Unfortunately, limited studies focus on the change in NLR[16,24] and mGPS.

The purpose of the present study was to investigate the prognostic factors and to evaluate the significance of these changes during chemotherapy in patients with APC.

MATERIALS AND METHODS

Study population and data collection

We retrospectively investigated the data of APC who received chemotherapy between January 2006 and December 2019 at Kofu Municipal Hospital and University of Yamanashi Hospital. All APC patients who were admitted during the research time were eligible for participation. Patients who underwent the only examination were excluded from the study. We retrieved patient records from a maintained database at our hospitals and performed a systematic retrospective review of patient diagnosis, treatment, and laboratory data. Laboratory assessment at baseline included complete blood cell count, serum biochemistry, and levels of serum tumor markers, such as CEA and CA19-9. The institutional review board of Kofu Municipal Hospital approved this study (approval code R2–3, July 15, 2020). Informed consent was obtained in the form of an opt-out on the website.

Prognostic variables

With reference to previous reports, we examined age, the presence or absence of distant metastasis, ECOG PS, CEA, CA19-9, mGPS, and NLR as potential prognostic factors.

mGPS score was calculated as follows: 2, elevated C-reactive protein (CRP) ($\geq$10 mg/L) and low albumin (<3.5 g/dL); 1,

elevated CRP only; and 0, normal CRP (<10 mg/L). Serum albumin and CRP concentration were measured before any kind of treatment. The NLR was determined by the neutrophil percentage value divided by the lymphocyte percentage value. ΔCEA (ΔCA19-9, ΔNLR, and ΔmGPS) was calculated by subtracting the baseline CEA (CA19-9, NLR, and mGPS) from the CEA (CA19-9, NLR, and mGPS) at the start of second cycles of chemotherapy (cycle 2-cycle 0). Based on our previous study,[8] high NLR was defined as 3.9. If infection and/or jaundice were present, these parameters were measured after symptoms had been relieved.

Treatment and related evaluation

Chemotherapy including regimen schedules and standard doses was adjusted at the discretion of the attending physician based on the incidence of adverse events or the general condition of the individual patient. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria by computed tomography scans at intervals of at least 3 months. Evaluation procedures were performed ahead of schedule if the patient's general condition worsened or severe adverse events occurred. Toxicity was graded according to the common terminology criteria for adverse events version 4.0 (CTCAE v4.0). OS was calculated from the date of chemotherapy initiation to that of death from any cause or it was censored at the last follow-up. Progression-free survival (PFS) was calculated from the date of chemotherapy initiation to that of progression or death from any cause, whichever occurred first, or was censored at the last follow-up.

Statistical analysis

Survival curves were estimated according to the Kaplan–Meier method, and differences were evaluated with the log-rank test. Variables that achieved statistical significance ($P < 0.05$) in univariate analysis were used for multivariate cox regression analysis to identify significant independent factors. We also calculated the hazard ratio (HR) and 95% confidence intervals. Significance was considered $P < 0.05$. All statistical analyses were run using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interfaces for R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

A total of 213 APC patients were investigated. Patient demographics are shown in Table 1. The median age at diagnosis was 72 years. Exactly 159 patients suffered from distant metastasis, and the remaining 54 patients had locally APC. First-line chemotherapy was gemcitabine alone in 56 patients, S-1 (oral fluoropyrimidine prodrug) alone in 30 patients, gemcitabine and S-1 combination therapy in 68 patients, gemcitabine and nab-paclitaxel combination therapy (GnP) in 55 patients, and FOLFIRINOX in 4 patients.

Table 1: Patient characteristics

Category	n=213, n (%)
Gender (%)	
Male	113 (53.1)
Female	100 (46.9)
Age at chemotherapy (years)	
Mean	69.9
Median (range)	72 (35-86)
ECOG PS	
0-1	184 (86.4)
2	29 (13.6)
Disease status	
Locally advanced	54 (25.4)
Distant metastasis	159 (74.6)
First-line chemotherapy	
Gem	56 (26.3)
S-1	30 (14.1)
GEM + S-1	68 (31.9)
GEM + nab-PTX/FOLFIRINOX	59 (27.7)
NLR	
Mean	3.67
Median (range)	2.83 (0.72-19.0)
<3.9	156 (73.2)
≥3.9	57 (26.8)
ΔNLR	
≤0	137 (64.3)
>0	76 (35.7)
mGPS	
0	147 (69.0)
1	32 (15.0)
2	34 (16.0)
ΔmGPS	
≤0	175 (82.2)
>0	38 (17.8)
CEA (ng/mL)	
<5.0	87 (40.8)
≥5.0	126 (59.2)
ΔCEA	
≤0	119 (55.9)
>0	94 (44.1)
CA19-9 (U/mL)	
<37.0	39 (18.3)
≥37.0	174 (81.7)
ΔCA19-9	
≤0	154 (72.3)
>0	59 (27.7)

ECOG PS: Eastern Cooperative Oncology Group Performance Status, CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, mGPS: Modified Glasgow prognostic score, NLR: Neutrophil-to-lymphocyte ratio, GEM+nab-PTX: Gemcitabine and nab-paclitaxel

Response and survival

No complete response was observed. Partial response rate was observed in 32 patients (15.0%), and stable disease was documented in 96 patients, so the disease control rate was 60.1%. The PFS was 5.4 months, and the OS was 10.3 months [Figure 1a]. There was no significant difference
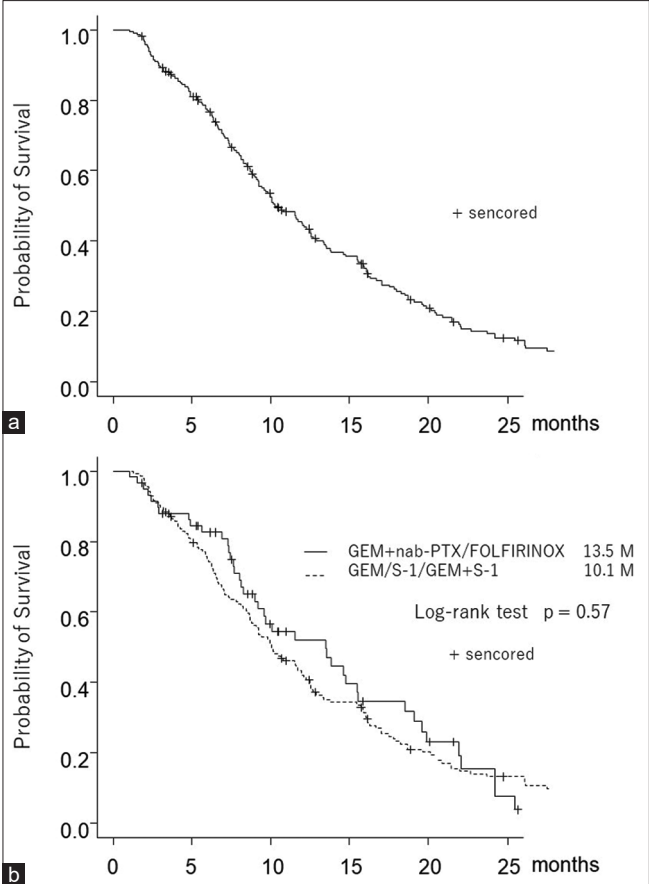

Figure 1: Kaplan–Meier estimates for overall survival (a) all patients; (b) according to treatment

between conventional chemotherapy (GEM, S-1 and GEM+S-1) and new regimens (GnP and FOLFIRINOX) [Figure 1b]. Rate of patients who received second-line therapy was 44%.

Prognostic variables

Exactly 126 patients (59.2%) had high CEA (≥5.0). ΔCEA >0 was found in 94 patients (44.1%). OS was significantly shorter in the high-baseline group and the CEA-worsening (>0) group compared with the other groups, whereas 124 patients (81.7%) had high CA19-9 (≥37.0). ΔCA19-9 >0 was found in 59 patients (27.7%). OS was significantly shorter in the high-baseline group and the CA19-9-worsening (>0) group compared with the other groups. The median baseline NLR was 2.83 and 57 patients (26.8%) had high NLR (≥3.9). ΔNLR >0 was found in 76 patients (35.7%). OS was significantly shorter in the high-baseline group and the NLR-worsening (>0) group, compared with the other groups. Baseline mGPS 1–2 was found in 66 patients (31.0%), and ΔmGPS >0 was found in 38 patients (17.8%). OS was significantly shorter in the mGPS 1–2 group, but there was no correlation with ΔmGPS and OS [Table 2].

Multivariate analysis to detect independent prognostic factors

First, we explored prognostic factors [Table 2]. ECOG PS 2 ($P < 0.001$), distant metastasis ($P = 0.03$), NLR ≥3.9

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Table 2: Univariate and multivariate analyses to detect independent prognostic factors

Variable	n	Survival month	Univariate P	Multivariate HR (95% CI)	P
Gender					
Male	113	10.5	0.92		
Female	100	10.3			
Age at chemotherapy (years)					
<75	138	10.5	0.78		
≥75	75	10.1			
ECOG PS					
0-1	184	12.0	<0.001	4.07 (2.44-6.79)	<0.001
2	29	5.3			
Disease status					
Locally advanced	54	13.5	0.03	1.23 (0.86-1.77)	0.26
Distant metastasis	159	9.4			
NLR					
<3.9	156	12.3	<0.001	1.97 (1.35-2.87)	<0.001
≥3.9	57	6.3			
mGPS					
0	147	13.5	<0.001	2.77 (1.95-3.93)	<0.001
1-2	66	5.7			
CEA (ng/mL)					
<5.0	87	12.5	0.02	1.44 (1.05-1.98)	0.026
≥5.0	126	9.6			
CA19-9 (U/mL)					
<37.0	39	14.6	0.03	1.83 (1.21-2.77)	0.004
≥37.0	174	9.7			
First-line chemotherapy					
GEM/S-1/GEM + S-1	154	10.0	0.57		
GEM + nab-PTX/FOLFIRINOX	59	13.5			
ΔNLR					
≤0	137	12.5	0.003	2.01 (1.47-2.77)	<0.001
>0	76	8.2			
ΔmGPS					
≤0	175	11.5	0.94		
>0	38	8.6			
ΔCEA					
≤0	119	12.5	0.001	1.64 (1.19-2.24)	0.002
>0	94	9.1			
ΔCA19-9					
≤0	154	12.3	0.003	1.77 (1.25-2.53)	0.002
>0	59	7.4			

CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, mGPS: Modified Glasgow prognostic score, NLR: Neutrophil-to-lymphocyte ratio, GEM+nab-PTX: Gemcitabine and nab-paclitaxel, ECOG PS: Eastern Cooperative Oncology Group Performance Status, HR: Hazard ratio, CI: Confidence interval

($P < 0.001$), mGPS 1–2 ($P < 0.001$), CEA ≥5.0 ($P = 0.02$), CA19-9 ≥37 ($P = 0.03$), ΔNLR >0 ($P = 0.003$), ΔCEA >0 ($P = 0.001$), and ΔCA19-9 >0 ($P = 0.003$) were extracted from univariate analysis. Multivariate analysis was undertaken to identify pretreatment variables that correlated with OS, which revealed that ECOG PS 2 (HR 4.07, $P < 0.01$), NLR ≥ 3.9 (HR 1.97, $P < 0.001$), mGPS 1–2 (HR 2.77, $P < 0.001$), CEA ≥5.0 (HR 1.44, $P = 0.026$), CA19-9 ≥37 (HR 1.83, $P = 0.004$), ΔNLR >0 (HR 2.01, $P < 0.001$), Δ EA >0 (HR 1.64, $P = 0.002$), and ΔCA19-9 >0 (HR 1.77, $P = 0.002$) were independent negative prognostic factors.

Combining baseline and change during chemotherapy

Combining both baseline CEA and ΔCEA, we categorized patients according to the two prognostic factors; Group A (CEA <5.0 and ΔCEA≤0), Group B (CEA<5.0 and ΔCEA>0), Group C (CEA≥5.0 and ΔCEA≤0), and Group D (CEA≥5.0 and ΔCEA>0). Patients in Group B, Group C, and Group D had significantly shorter OS compared to Group A [Figure 2a]. The same analysis was performed for CA19-9, a similar tendency was obtained, but there was no significant difference [Figure 2b]; otherwise, a significant difference was observed for NLR [Figure 2c].
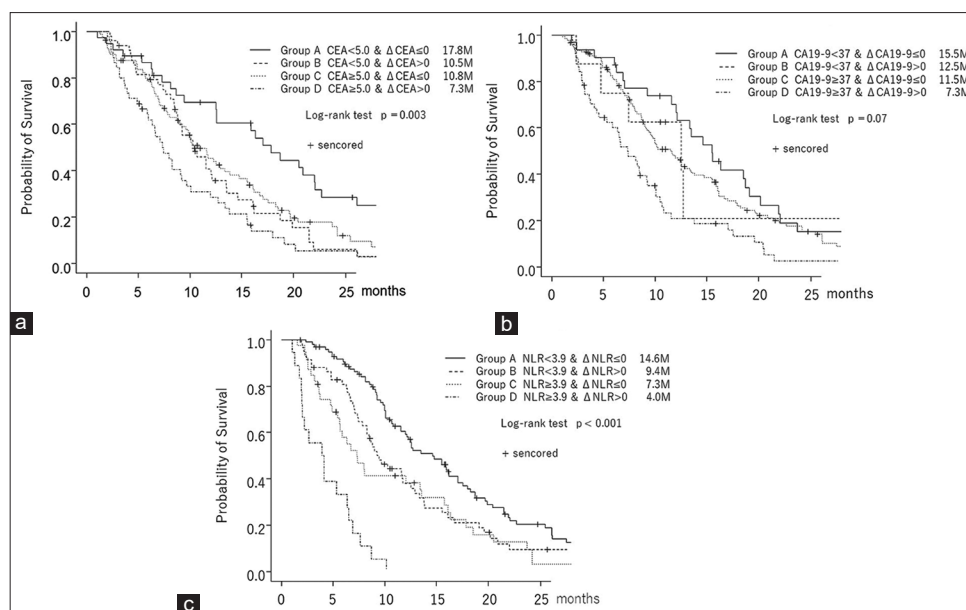
Figure 2: Kaplan–Meier estimates for overall survival according to four risk groups (a) combining baseline CEA and ΔCEA; (b) combining baseline CA19-9 and ΔCA19-9; (c) combining baseline NLR and ΔNLR. CEA: Carcinoembryonic antigen, NLR: Neutrophil-to-lymphocyte ratio, CA19-9: Carbohydrate antigen 19-9

Discussion

Our study found that ECOG PS, CEA, CA19-9, mGPS, and NLR were independent prognostic factors in patients with APC. Besides, we noted the independent prognostic value of ΔCEA, ΔCA19-9, and ΔNLR in APC.

Essentially, it is considered that tumor marker reflects tumor burden and the spread of disease. The OS in patients treated with combination chemotherapy was similar to that with single-agent chemotherapy in the high CEA.[9] Many published reports have considered the clinical utility of serum CA19-9 as a prognostic marker in various situations, and a decline in CA19-9 level from baseline to the time of response evaluation is considered prognostic.[5,19-23] However, most studies investigating the prognostic role of CA19-9 kinetics were retrospective and study cohorts were heterogeneous. The cutoff values of CA19-9 decline for OS were varied, and the timing of the CA19-9 measurements was also varied in each study. In this study, we found that not only CEA and CA19-9 at the start of treatment but also these changes were factors of OS in patients with APC.

To date, studies have shown that higher NLR correlated with adverse survival outcomes in patients with APC.[4,8,16,17] High NLR is often caused by elevated neutrophil levels and relative lymphocytopenia. High neutrophil levels can hasten tumor cell progression by upregulating a variety of inflammatory cytokines and providing a suitable microenvironment for tumor growth.[25,26] Furthermore, lymphocytopenia causing from many inhibitory immunological mediators emitted by tumor cells represents an immunosuppressive condition in cancer patients and contributes to a poorer outcome.[27] Therefore, NLR is considered to reflect a balance between the tumor-promoting environment and the anti-tumor immune status, so the reduction of NLR due to chemotherapy correlates with prolonged OS is reasonable. To minimize the effects of myelosuppression due to chemotherapy and to switch to second-line chemotherapy or the best supportive care timely, the blood findings at the beginning of the second cycle of chemotherapy were adopted. The mGPS also was a useful systemic inflammatory prognostic factor in this study, but its change was not correlated with OS. The reason might be due to mGPS being a three-level evaluation so the detection power might be weaker over time.

Several studies also have shown that combination of NLR and CA 19-9 could be a prognostic marker in patients with pancreatic cancer.[14,28,29] Recently, combination of an 18% decline of CA19-9 and posttreatment NLR <2.62 could improve prognostic accuracy in APC treated with first-line systemic chemotherapy.[30] In this study, we found that a combination of baseline and change of CEA or NLR also could improve prognostic accuracy.

The limitations of this study included (i) retrospective design; so we did not have control over accurate record keeping, as well as being prone to recall bias; (ii) lack of considering the prognostic impact of second-line chemotherapy; and (iii) this study was conducted only in the Japanese population.

Conclusion

We found the significance of baseline and change in the tumor markers, along with the neutrophil-to-lymphocyte ratio in predicting OS in APC patients' who underwent chemotherapy. Our results suggest that the evaluation of these factors is helpful in OS prediction and chemotherapy

adjustment. Thus, further validation in a prospective study is warranted.

Conflicts of interest

There are no conflicts of interest.

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