Usefulness of palliative prognostic score in the treatment of patients with non-resectable gastric cancer

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Abstract. The aim of this study was to evaluate the clinical usefulness of the palliative prognostic (PaP) score in patients with non-resectable advanced gastric cancer. The PaP score was calculated prior to each course of chemotherapy in 44 consecutive patients with non-resectable advanced gastric cancer between 2003 and 2010 at the Tottori University Hospital, Yonago, Japan. The prognosis was evaluated according to the PaP score and the different chemotherapeutic agents. The median survival time (MST) was 10 months. The PaP score classified the heterogeneous patient sample into three isoprognostic groups with regard to the possibility of a 1-month survival period, with 28 patients in group A (>70% chance), 12 in group B (30-70% chance) and 4 in group C (<30% chance). The MST of the three groups was 11, 3 and 1 months for group A, B and C, respectively. In group A, chemotherapeutic regimens did not affect patient survival, although the docetaxel regimen prolonged survival of patients in group B. In conclusion, the PaP score may be useful in selecting the best chemotherapeutic regimen in patients with non-resectable gastric cancer.

Introduction

Outcomes are extremely poor in patients with non-resectable gastric cancer, with a median survival period ranging from 3 to 5 months, even with the best supportive care (1,2). S-1 is an oral anticancer drug that combines tegafur, a prodrug of fluorouracil, with 5-chloro-2,4-dihydropyrimidine (CDHP) and potassium oxonate at a molar ratio of 1:0.4:1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) (3). In a phase II study of S-1, an ~40% response rate was noted in patients with advanced gastric cancer (4,5). Thus, S-1 chemotherapy has been widely used as a basic treatment for patients with non-resectable gastric cancer. Findings from the SPIRIT trial identified S-1 plus cisplatin as a standard first-line treatment (6) and recommended its use in patients with an expected survival period of at least 3 months. However, due to the severe side effects, the S-1 plus cisplatin regimen [S-1: 40-60 mg/m^2; in a 5-week cycle (3 weeks on and 2 weeks off), in combination with 60 mg/m^2 cisplatin on day 8] was difficult to continue in patients with poor Eastern Cooperative Oncology Group Performance Status (ECOG PS). Additionally, a number of patients suffered from reduced quality of life (QOL) while undergoing this medical treatment (7). However, Casaretto *et al* (8) reported that chemotherapy increased the 1-year survival rate, provided a longer symptom-free period and improved the QOL of patients with non-resectable advanced gastric cancer. Clinically, it is important to select chemotherapeutic regimens that are most appropriate for the patient's condition.

The objective indicators determining suitable chemotherapy regimens for patients with non-resectable gastric cancer have been studied. The standard prognostic indicators in oncology, such as tumor size, grade and stage, or molecular biology, are less relevant in patients with advanced cancer. The palliative prognostic (PaP) score was developed in the 1990s, as a result of a series of prospective trials aimed to identify clinical and biologic factors associated with the prognosis of advanced cancer patients referred to hospice and to merge them into a prognostic index (9). The survival of patients with non-resectable or recurrent cancers can be estimated using the PaP score even during chemotherapy (10).

In this study, the usefulness of the PaP score in determining the first-line chemotherapy for patients with non-resectable gastric cancer was examined retrospectively.

Materials and methods

Patients. Between 2003 and 2010, 558 patients with gastric cancer were treated at the Tottori University Hospital, Yonago, Japan. Forty-four patients (7.9%) were diagnosed as non-resectable. Details of these 44 patients are shown in Table I. Patients were followed up at the hospital until March 2012. During this period, gastrectomy was performed on 3 patients (bleeding, 2 patients; perforation, 1 patient). All participants provided informed consent and the study design was approved by the Ethics Review Board of Tottori University.

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Table I. Patient data (n=44).

Variables	No.
Age (range, mean; years)	23-92, 66.5
Gender (male/female)	24/20
Ascites (yes/no)	10/34
ECOG PS (0/1/2)	14/18/12
Non-resectable parameters	
Locally advanced	6
Lymph node	12
Hematogenic metastasis	19
Peritoneal metastasis	20
Surgical intervention	
No	29
Probe-laparotomy	1
Bypass operation	11
Gastrectomy	3

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table II. PaP score.

Item	Score
Symptoms (presence/absence)	
Anorexia	1.0/0.0
Dyspnea	1.5/0.0
Karnofsky performance status	
≥ 50	0.0
30-40	0.0
10-20	2.5
Clinical prediction of survival (weeks)	
>12	0.0
11-12	2.0
9-10	2.5
7-8	2.5
5-6	4.5
3-4	6.0
1-2	8.5
Total white blood cells (/mm^3)	
Normal (4,800-8,500)	0
High (8,501-11,000)	0.5
Very high (>11,000)	1.5
Lymphocyte percentage	
Normal (20.0-40.0)	0
Low (12.0-19.9)	1.0
Very low (0-11.9)	2.5
PaP score groups	
A	0-5.5
B	5.6-11.0
C	11.1-17.5

PaP, palliative prognostic.

Chemotherapy. First-line chemotherapy was received by 41 patients (S-1, 7; S-1 plus cisplatin, 17; S-1 plus docetaxel, 13; other chemotherapy, 4). Chemotherapy was terminated in the case of 3 patients with poor performance status (PS) and advanced age, who then received best supportive care (BSC).

PaP score. The PaP score has four criteria: two symptoms (anorexia and dyspnea), performance status measured by the Karnofsky performance score, white blood cells (WBC) abnormalities (high total WBC count and lymphopenia) and a physician's survival prediction measured in weeks (Table II). Validated cut-off points based on the total PaP score were established to classify the patients into three prognostic groups for survival at 30 days: group A (>70% probability of a 1-month survival period), 0 to 5.5 points; group B (30-70% probability of a 1-month survival period), 5.6 to 11 points; group C (<30% probability of a 1-month survival), 11.1-17.5 points (10,11) (Table II).

Statistical analysis. The terminology used in this study conforms to the Japanese Classification of Gastric Carcinoma, 3rd English edition (12). Statistical analysis was carried out using χ^2 tests. Overall survival was calculated from the time of enrolment to death. Median survival time (MST) was calculated using the Kaplan-Meier non-parametric test, while comparison between the different patient cohorts was performed using the log-rank test. P<0.05 was considered to indicate a statistically significant difference.

Results

Median survival time. The MST of the 44 patients was 10 months. Patients were divided into 3 subgroups, according to their PaP score. The MST of 28 patients in group A

(11 months) was much better compared to the 12 patients in group B (3 months) or the 4 patients in group C (1 month, P<0.0001, Fig. 1). In the 40 patients in groups A and B, the correlation between prognosis and factors considered to affect the prognosis was analyzed (Table III). The presence or absence of ascites or bypass surgery did not affect patient survival.

Correlation between the PaP score and the first-line chemotherapy regimens. The correlation between the PaP score and the first-line chemotherapy regimens are shown in Table IV. The S-1 plus cisplatin regimen was commonly used as first-line chemotherapy in PaP group A. However, due to renal dysfunction, cisplatin was not used in a number of patients in group B, thus S-1 plus docetaxel or S-1 alone was selected in this group instead. In the 28 patients in group A, the MST using the cisplatin regimen (10 months, n=16) did not differ from the other regimens (11 months, n=12, P=0.221). Although the difference was not significant (P=0.062), in the 12 patients

Table III. Prognosis of patients in PaP score groups A and B.

	N	MST (months)	P-value
PaP score group			
A	28	11	0.0045
B	12	3	
Ascites			
Absent	31	10	0.7548
Present	9	10	
Surgical intervention			
No	25	10	0.7238
Yes	15	11	

PaP, palliative prognostic; MST, median survival time.

Table IV. Correlation between PaP score and first-line chemotherapy.

First-line chemotherapy	PaP score group		
	A	B	C
S-1 plus cisplatin	16	1	0
S-1 plus docetaxel	8	5	0
S-1 plus CPT-11	2	2	0
S-1 only	2	4	1
BSC	0	0	3

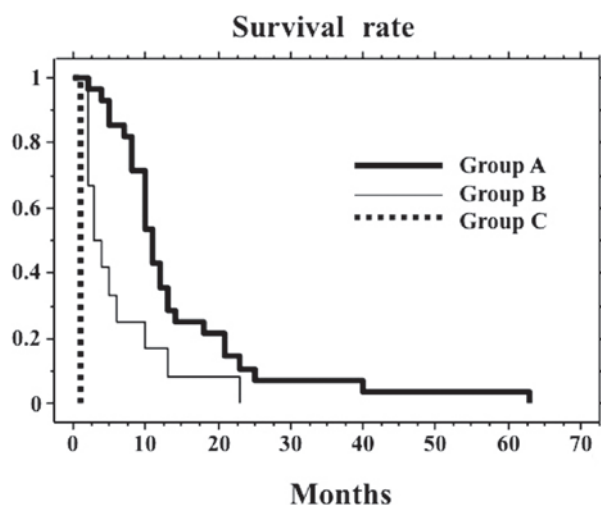PaP, palliative prognostic; BSC, best supportive care.

Figure 1. Survival of patients in group A was much better compared to patients in group B or C (P<0.0001).
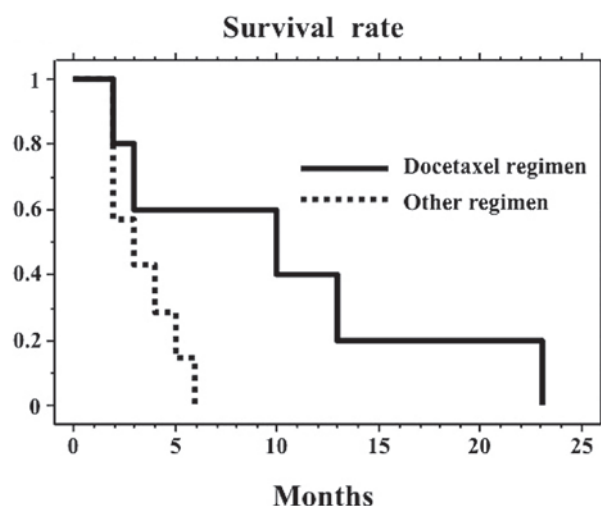

Figure 2. Survival of the 5 patients treated with docetaxel was better compared to the 7 patients treated with other regimens in the PaP group B, with no statistically significant difference (P=0.062).

in group B, the docetaxel regimen prolonged the survival from 3 (other regimens, MST, 3 months, n=7) to 10 months (docetaxel regimen, MST, 10 months, n=5, Fig. 2).

Discussion

Large-scale randomized phase III clinical trials may reveal effective chemotherapeutic regimens for patients with advanced cancers, with the exception of those of advanced age or with poor PS. However, in clinical situations, it is difficult to decide the most suitable chemotherapeutic regimen for patients with short life expectancy or poor PS, such as patients with non-resectable gastric cancer. Identifying the patients that may benefit from palliative chemotherapy is quite difficult and its usefulness when controlling symptoms and maintaining QOL has not yet been proven (13,14).

The PaP score contains five parameters (symptom, PS, inflammation, immunity and physician's survival prediction) associated with cancer patient survival. Findings of previous studies have indicated that the PaP score may accurately estimate pre-terminal patient survival (15-17). Using the PaP score in 44 patients with non-resectable advanced gastric cancer, the correlation between PaP score groups and chemotherapeutic regimens was investigated. The findings showed that in the PaP score group A, the S-1 plus cisplatin regimen was commonly used and differences in chemotherapeutic regimens did not affect the survival of the patients in this group. In comparison, the survival of patients in PaP group B was extremely poor, although the S-1 plus docetaxel regimen prolonged the survival of these patients from 3 to 10 months. Although this study is retrospective and the number of objective cases is small, the docetaxel regimen may have a survival advantage in patients with a poor prognosis.

Docetaxel is reported to have a low rate of grade 3/4 leucopenia and neutropenia (19.4 and 10.6%) and rare, severe non-hematologic toxicities (18). Docetaxel chemotherapy with or without S-1 has been a suitable treatment for patients with advanced gastric cancer, advanced age or poor PS (19).

In conclusion, in the treatment of advanced non-resectable gastric cancer, the PaP score should be used to select patients and chemotherapeutic regimens. The S-1 plus docetaxel regimen is expected to improve outcomes in patients with a poor PS.

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