Neutropenia as a prognostic factor and safety of second-line therapy with S-1 for advanced or recurrent pancreatic cancer

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Abstract. The aim of this retrospective study was to investigate the safety of S-1 as second-line therapy and to evaluate the association between neutropenia occurring during first-line gemcitabine (GEM) therapy and survival for advanced or recurrent pancreatic cancer (APC). Between January, 2010 and December, 2014, 123 APC patients received chemotherapy at the Ogaki Municipal Hospital (Ogaki, Japan). Of those, 37 received GEM as first-line and S-1 as a second-line therapy (GEM→S-1 group). A further 60 patients received GEM as first-line therapy, but did not receive second-line therapy (GEM group). The median overall survival in the GEM→S-1 (n=37) and GEM (n=60) groups was 323 days [95% confidence interval (CI): 138-218.9 days] and 172 days (95% CI: 105-184.4 days), respectively (P=0.0004). The median overall survival in the mild (grade ≤2; n=63) and severe (grade ≥3; n=34) neutropenia groups was 178 days (95% CI: 182-275 days) and 330 days (95% CI: 297-514 days), respectively (log-rank test, P=0.0023). The severe non-haematological toxicities associated with S-1 as second-line therapy were nausea (2.7%) and hand-foot syndrome (2.7%). Second-line S-1 treatment was discontinued due to adverse events in 5.4% (2/37) of the cases. In conclusion, neutropenia occurring during GEM therapy administered as first-line treatment to APC patients was strongly associated with a better prognosis. S-1 therapy as second-line treatment was associated with a low incidence of severe adverse events and the patients were able to successfully continue treatment.

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Introduction

Pancreatic cancer has the worst prognosis among all refractory gastrointestinal cancers. According to data on the number of site-specific cancer deaths in Japan, pancreatic is the fourth most common cancer, after lung, stomach and colon cancers (1). In 1997, randomised clinical trials comparing gemcitabine (GEM) and 5-fluorouracil (5-FU) chemotherapy for pancreatic cancer (2), demonstrated that GEM was more beneficial for symptom relief compared with 5-FU, and also prolonged survival. In addition, since August, 2006, an oral 5-FU formulation containing tegafur, gimeracil and oteracil potassium (S-1) has been approved by insurance companies for the treatment of pancreatic cancer. The GEM and S-1 trial (GEST study) demonstrated that S-1 was non-inferior to GEM, but did not prove the superiority of combination therapy with GEM and S-1 (3). Therefore, GEM or S-1 is recommended for standard chemotherapy of advanced or recurrent pancreatic cancer (APC).

The incidence of myelosuppression, such as neutropenia, in first-line GEM therapy is high, which may delay treatment and affect prognosis. Moreover, neutrophil count (4,5) and the ratio of neutrophils to lymphocytes (6,7) have been reported to be prognostic factors for APC patients. In addition, it has been reported that neutropenia is a prognostic factor in gastric (8) and colon cancers (9), as well as haematopoietic tumours (10). However, due to the poor prognosis of pancreatic cancer, the association between neutropenia and prognosis, and details such as dose and relative dose intensity (RDI), have not been investigated in the clinical setting. Furthermore, in the GEST study (3), gastrointestinal symptoms such as nausea, diarrhoea and stomatitis have been frequently observed among adverse events (AEs) associated with S-1 monotherapy. Thus, when administering S-1 as second-line therapy, tolerability to AEs may be reduced, with deterioration of the patient's condition. The frequency of AEs and treatment continuity associated with second-line S-1 chemotherapy have not been extensively investigated (11-14). We previously reported that albumin (Alb) levels <3.5 g/dl and creatinine clearance levels <78 ml/min were risk factors for treatment discontinuation or dosage reduction of S-1 in gastric cancer chemotherapy (15,16).

Therefore, this retrospective study aimed to investigate the safety of S-1 as second-line therapy for APC patients. In

addition, we evaluated the association between neutropenia occurring during first-line GEM therapy and survival.

Subjects and methods

Subjects and methods. Between January, 2010 and December, 2014, 123 patients received chemotherapy for APC at the Ogaki Municipal Hospital (Ogaki, Japan). Of those, 37 received GEM as first-line and S-1 as second-line therapy (GEM→S-1 group). A further 60 patients received GEM as first-line therapy, but did not receive second-line therapy (GEM group). Age, RDI, administration period, AEs and reasons for dose reduction or temporary suspension of medication were retrospectively surveyed for each patient. In addition, patients receiving ongoing treatment with GEM or S-1 during the study period were excluded. The dates of AEs and reasons for discontinuation of chemotherapy were extracted from electronic charts. The severity of AEs was classified according to the Common Terminology Criteria for Adverse Events, version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_ 2010-06-14_QuickReference_5x7.pdf). The present study was approved by the Institutional Review Board of Ogaki Municipal Hospital.

Doses and routes of GEM and S-1 therapies. GEM was administered intravenously at a starting dose of 1,000 mg/m^2 over 30 min, weekly, on days 1, 8 and 15 over a 4-week period. S-1 was orally administered for 4 weeks (dose: <1.25 m^2 of body surface area, 80 mg/d; 1.25-1.5 m^2, 100 mg/d; ≥1.5m^2, 120 mg/d), followed by a 2-week washout period.

Statistical analysis. The F-test was performed to compare the two groups. Welch's t-test or the Chi-square test of independence (Fisher's exact probability test) was used to analyse the patients' characteristics (age, neutrophil count, RDI and dosage) shown in Table I. The Kaplan-Meier log-rank test was used to compare overall survival. In all these tests, P<0.05 was considered to indicate statistically significant differences. All statistical analyses were performed using JMP 8 software (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. The patients' characteristics are shown in Table I. In the GEM→S-1 and GEM groups, the median age was 68 years (range, 54-77 years) and 66.3 years (range, 43-83 years); the median neutrophil count was 3,650/μl (range, 1,610-7,740/μl) and 4,100/μl (range, 1,800-9,290/μl (P=0.0431); the RDI was 90.4% (range, 36.9-100%) and 83.4% (range, 53.0-100%); and the dosage used was 100% (range, 74.6-100%) and 100% (range, 77.1-100%), respectively.

Overall survival in the GEM→S-1 and S-1 groups. The Kaplan-Meier survival curves for the cohorts (n=97) are shown in Fig. 1. The median overall survival of the GEM→S-1 (n=37) and GEM (n=60) groups were 323 days [95% confidence interval (CI): 138-218 days] and 172 days (95% CI: 105-184 days), respectively (log-rank test, P=0.0004).

Overall survival according to the highest grade of neutropenia following first-line therapy with GEM. The Kaplan-Meier survival curves showing the highest grade of neutropenia following first-line therapy with GEM (n=97) are shown in Fig. 2. The median overall survival time in the mild (grade ≤2; n=63) and severe (grade ≥3; n=34) neutropenia groups was 178 days (95% CI: 182-275 days) and 330 days (95% CI: 297-514 days), respectively (log-rank test, P=0.0023). In addition, the frequency of grade 3 or 4 neutropenia in the GEM→S-1 group (48.6%, 18/37 cases) was significantly higher compared with that in the GEM group (26.7%, 16/60 cases; P=0.0238).

Reasons for discontinuation, postponement and dose reduction. The reasons for discontinuation, postponement and dose reduction in the GEM→S-1 and GEM groups are shown in Table II. In the GEM→S-1 group, GEM administration was interrupted due to progressive disease (PD) in 36 cases, or AEs in 1 case. S-1 discontinuation occurred due to changes in performance status (PS), PD, AEs (diarrhoea and anorexia), and other reasons in 21, 13, 2 and 1 cases, respectively. In addition, GEM administration was postponed due to haematological and non-haematological toxicities in 22 and 4 cases, respectively, and other reasons in 1 case. S-1 administration was postponed due to haematological toxicities in 3 cases; non-haematological toxicities in 6 cases (diarrhoea, stomatitis, skin hyperpigmentation, constipation, anorexia and vomiting); a decrease in PS in 2 cases; due to the patient's wishes in 1 case; and other reasons in 3 cases.

In the GEM group, the dosage was reduced due to a decrease in PS, myelosuppression, renal failure and other reasons in 8, 1, 1 and 1 cases, respectively.

Main adverse events of second-line therapy with S-1. The main AEs caused by second-line therapy with S-1 are shown in Table III. The most common haematological toxicities were oligochromemia (14 cases, 37.8%), leukopenia (7 cases, 18.9%) and neutropenia (6 cases, 16.2%). Non-haematological toxicities included anorexia (7 cases, 18.9%), diarrhoea (7 cases, 18.9%), malaise (6 cases, 16.2%), stomatitis (6 cases, 16.2%), nausea (5 cases, 13.5%), watery eyes (5 cases, 13.5%) and skin hyperpigmentation (4 cases, 10.8%).

Association between the incidence of gastrointestinal toxicity and serum Alb in second-line therapy with S-1. Following second-line S-1 therapy in the GEM→S-1 group, the frequency of grade 2, 3 or 4 malaise and digestive system disorders in subjects with Alb <3.5 g/dl (10/14 cases) were significantly higher compared with those with Alb ≥3.5 g/dl (2/23 cases; P=0.0002). In patients where treatment was interrupted due to diarrhoea and nausea (2 cases), the Alb levels were 3.3 and 3.2 g/dl, respectively. In addition, S-1 therapy was postponed in 6 cases due to AEs such as diarrhoea, stomatitis, skin hyperpigmentation, anorexia and nausea. In 5 of 6 of these cases, the Alb level was ≤3.5 g/dl.

Discussion

The aim of this retrospective study was to investigate the safety of S-1 as second-line therapy, and to evaluate the association

Table I. Patient characteristics.

Characteristics	Patients who received second-line treatment: GEM→S-1 (n=37)	Patients who did not receive second-line treatment: GEM (n=60)	P-value
Age, years (range)	68 (54-77)	66.3 (43-83)	0.3738
Gender, n			0.4681
Female	18	31	
Male	19	29	
BSA, m^2	1.45 (1.12-1.93)	1.48 (1.22-1.81)	0.5942
CrCl, ml/min	74.5 (43.2-120.9)	76.1 (21.7-150.4)	0.9632
Disease stage, n			0.0845
IVa	19	21	
IVb	18	39	
Disease status, n			0.0090
Unresectable	22	50	
Recurrent	15	10	
Neutrophils, /μl	3,650 (1,610-7,740)	4,100 (1,800-9,290)	0.0431
RDI of GEM (range)	90.4 (36.9-100)	83.4 (53.0-100)	0.1162
Administration period of GEM, days (range)	159 (48-574)	95 (7-882)	0.2759
Dosage of GEM, %	100 (74.6-100)	100 (77.1-100)	0.9264
Metastatic site, n			0.2308
Liver	12	25	
Lung	4	3	
Peritoneum	2	10	
Lymph nodes	3	8	
Other	1	9	
Complications, n			0.2959
Hypertension	17	16	
Hyperlipidaemia	6	3	
Diabetes	13	16	
Asthma	5	1	

GEM, gemcitabine; S-1, tegafur, gimeracil, and oteracil potassium; BSA, body surface area; CrCl, creatinine clearance; RDI, relative dose intensity; GEM→S-1, group, patients who received GEM as first-line therapy and S-1 as second-line therapy; GEM group, patients who received GEM as first-line therapy and did receive second-line therapy.

between neutropenia occurring during first-line GEM therapy and survival in APC patients.

It has been reported that second-line treatment with S-1 monotherapy is associated with a better prognosis in APC patients (4,12-14). Similarly, this study has demonstrated that it is important to use GEM and S-1 for the treatment of APC. Furthermore, a study by Shitara *et al* (8) reported that neutropenia occurring during weekly paclitaxel treatment administered as second-line therapy to advanced gastric cancer patients is strongly associated with a better prognosis. In this study, the prognosis of APC patients with grade ≥3 neutropenia during first-line GEM therapy was good.

Regarding the association between neutropenia and prognosis, Shitara *et al* (8) hypothesized that neutropenia, an indicator of bone marrow suppression caused by a specific dose of a chemotherapeutic agent, may also be a surrogate marker indicating that the same dose is adequate for exerting an antitumor effect. If neutropenia is not present, it is possible that the patient has been administered too low a dose. In our study, no significant differences were found between the GEM→S-1 and GEM groups with regard to RDI and dose, or when the dosages were reduced. However, the neutrophil count was high in the GEM group at the start of treatment. Fridlender *et al* (17) reported that neutrophils are involved in vascularisation and are associated with cancer metastasis and angiogenesis. Hatori *et al* (4) reported that the number of neutrophils present prior to the first GEM treatment is a prognostic factor. Additionally, it has been reported that

Table II. Reasons for treatment discontinuation, postponement and dose reduction.

A, GEM→S-1 group

Reason for discontinuation			Reason for postponement			Reason for dose reduction		
	GEM	S-1		GEM	S-1		GEM	S-1
Progressive disease	36	13	Adverse events			Decrease in PS	2	7
			Hematological toxicity	22	3	Myelosuppression	8	1
Adverse events	1	2	Non-hematological toxicity	4	6	Non-hematological toxicity	0	4
Decrease in PS	0	21	Decrease in PS	0	2	Other	2	0
Other	0	1	Subject's wishes	0	1			
			Other	1	3			

B, GEM group

Reason for discontinuation		Reason for postponement		Reason for dose reduction	
Progressive disease	36	Adverse events		Decrease in PS	8
		Hematological toxicity	27	Myelosuppression	1
Adverse events	7	Non-hematological toxicity	21	Non-hematological toxicity	0
Decrease in PS	14	Decrease in PS	4	Renal function degeneracy	1
Other	6	Other	3	Other	0

PD, progressive disease; PS, performance status; GEM, gemcitabine; S-1, tegafur, gimeracil and oteracil potassium. GEM→S-1 group, patients who received GEM as first-line therapy and S-1 as second-line therapy. GEM group, patients who received GEM as first-line therapy and did not receive second-line therapy.

Table III. Adverse events following second-line therapy with S-1.

Adverse events	Grade 1	2	3	4	All grades (%)	Grade ≥3 (%)
Oligochromemia	1	9	4	0	14 (37.8)	4 (10.8)
Leukopenia	4	2	1	0	7 (18.9)	1 (2.7)
Neutropenia	2	2	2	0	6 (16.2)	2 (5.4)
AST/ALT increase	3	0	1	0	4 (10.8)	1 (2.7)
Blood bilirubin increase	2	1	0	0	3 (8.1)	0 (0.0)
Creatinine increase	1	2	0	0	3 (8.1)	0 (0.0)
Anorexia	4	3	0	0	7 (18.9)	0 (0.0)
Diarrhoea	3	4	0	0	7 (18.9)	0 (0.0)
Malaise	4	2	0	0	6 (16.2)	0 (0.0)
Stomatitis	4	2	0	-	6 (16.2)	0 (0.0)
Nausea	3	1	1	0	5 (13.5)	1 (2.7)
Watering eyes	5	0	0	-	5 (13.5)	0 (0.0)
Skin hyperpigmentation	4	0	-	-	4 (10.8)	0 (0.0)
Rash	3	0	0	0	3 (8.1)	0 (0.0)
Hand-foot syndrome	2	0	1	0	3 (8.1)	1 (2.7)
Oedema	1	2	0	0	3 (8.1)	0 (0.0)

S-1, tegafur, gimeracil and oteracil potassium; AST, aspartate aminotransferase; AST, alanine aminotransferase.

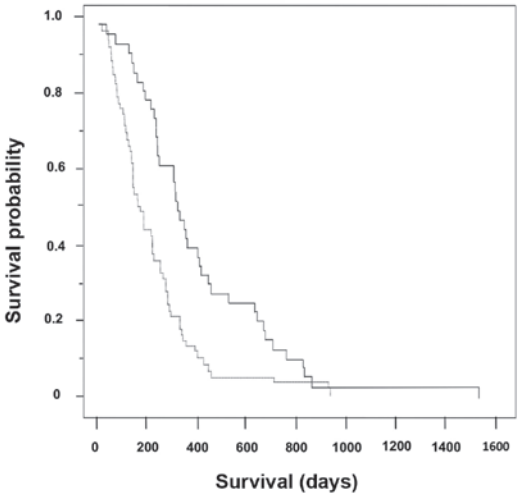

Figure 1. Kaplan-Meier survival curves of overall survival in the gemcitabine (GEM)→S-1 and GEM groups. Solid line, GEM→S-1group. Median survival time (MST), 323 (64-1514) days. Dotted line, GEM group. MST, 172 (33-918) days.

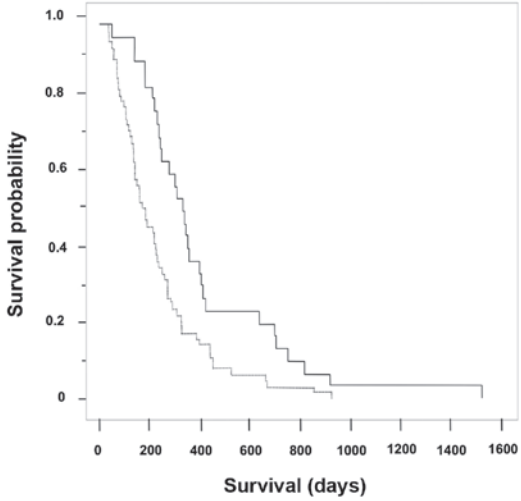

Figure 2. Kaplan-Meier survival curves showing the highest grade of neutropenia following first-line therapy with gemcitabine (GEM). Solid line, patients who had severe neutropenia (grade ≥3) during treatment with GEM. Median survival time (MST), 330 (47-1514) days. Dotted line, patients who had mild neutropenia (grade ≤2) during treatment with GEM. MST, 178 (33-918) days.

pharmacodynamics rather than pharmacokinetics determines the effect of GEM on survival.

Therefore, we recommend avoiding dosage reduction when the neutrophil count is high. These findings may aid future evaluation of dose escalation in patients without neutropenia to prolong survival. Prospective trials are required to assess whether dosing adjustments based on neutropenia may improve chemotherapeutic efficacy.

Regarding the safety of second-line therapy with S-1, grade ≥3 haematological toxicities were observed, but non-haematological toxicities were rarely recorded. The main AEs observed following second-line therapy with S-1 included haematological toxicities, such as oligochromemia (37.8%), leukopenia (18.9%) and neutropenia (16.2%), and non-haematological toxicities, such as anorexia (18.9%), diarrhoea (18.9%), malaise (16.2%) and stomatitis (16.2%), which were also reported by Todaka *et al* (18). In addition, of the 37 patients who received S-1 therapy, treatment was discontinued in 2 cases due to non-haematological toxicities (diarrhoea and anorexia). By contrast, in 6 cases with

non-haematological toxicities, such as diarrhoea, stomatitis, hand-foot syndrome, constipation, anorexia and vomiting, S-1 therapy was safely continued by postponing treatment. However, during second-line therapy with S-1, the frequency of grade ≥2 fatigue and gastrointestinal toxicity was 27.0% (10/37 cases) in patients with Alb levels <3.5 g/dl. This result is similar to that of previous studies (15,16) and should be considered when treating patients with S-1, as it may affect the treatment course. Similarly, fatigue and gastrointestinal toxicity in APC chemotherapy patients with Alb levels <3.5 g/dl must be carefully considered when planning the chemotherapy protocol.

In conclusion, neutropenia occurring when GEM is administered as first-line treatment to APC patients is strongly associated with a better prognosis. S-1 therapy as second-line treatment has been associated with a low incidence of severe AEs and the patients were able to successfully continue treatment.

References

1. Matsuda T, Ajiki W, Marugame T, Ioka A, Tsukuma H and Sobue T; Research Group of Population-Based Cancer Registries of Japan: Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: A chronological and international comparative study. Jpn J Clin Oncol 41: 40-51, 2011.
2. Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, *et al*: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. J Clin Oncol 15: 2403-2413, 1997.
3. Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N, Fukutomi A, Sugimori K, Baba H, Yamao K, *et al*: Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol 31: 1640-1648, 2013.
4. Hatori M, Tsuji D, Taku K, Daimon T, Kamezato M, Ikeda M, Makuta R, Hayashi H, Inoue K and Itoh K: Prognostic factors in patients with unresectable pancreatic cancer treated with gemcitabine: a retrospective analysis. Jpn J Pharm Health Care Sci 40: 734-741, 2014.
5. Teramukai S, Kitano T, Kishida Y, Kawahara M, Kubota K, Komuta K, Minato K, Mio T, Fujita Y, Yonei T, *et al*: Pretreatment neutrophil count as an independent prognostic factor in advanced non-small-cell lung cancer: An analysis of Japan Multinational Trial Organisation LC00-03. Eur J Cancer 45: 1950-1958, 2009.
6. An X, Ding PR, Li YH, Wang FH, Shi YX, Wang ZQ, He YJ, Xu RH and Jiang WQ: Elevated neutrophil to lymphocyte ratio predicts survival in advanced pancreatic cancer. Biomarkers 15: 516-522, 2010.
7. Stotz M, Gerger A, Eisner F, Szkandera J, Loibner H, Ress AL, Kornprat P, AlZoughbi W, Seggewiesn FS, Lackner C, *et al*: Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer 109: 416-421, 2013.
8. Shitara K, Matsuo K, Takahari D, Yokota T, Shibata T, Ura T, Ito S, Sawaki A, Tajika M, Kawai H and Muro K: Nuetropenia as a prognostic factor in advanced gastric cancer patients undergoing second-line chemotherapy with weekly paclitaxel. Ann Oncol 21: 2403-2409, 2010.
9. Shitara K, Matsuo K, Oze I, Mizota A, Kondo C, Nomura M, Yokota T, Takahari D, Ura T and Muro K: Meta-analysis of neutropenia or leukopenia as a prognostic factor in patients with malignant disease undergoing chemotherapy. Cancer Chemother Pharmacol 68: 301-307, 2011.
10. Shitara K, Matsuo K, Takahari D, Yokota T, Inaba Y, Yamaura H, Sato Y, Najima M, Ura T and Muro K: Neutropaenia as prognostic factor in metastatic colorectal cancer patients undergoing chemotherapy with first-line FOLFOX. Eur J Cancer 45: 1757-1763, 2009.
11. Kawashima H, Itoh A, Ohno E, Nakamura M, Miyahara R, Ohmiya N, Hara K, Kanamori A, Itoh T, Taki T, *et al*: Prospective multicenter study to investigate the introduction rate of second-line S-1 in gemcitabine-refractory unresectable pancreatic cancer. Cancer Chemother Pharmacol 68: 677-683, 2011.
12. Nakai Y1, Isayama H, Sasaki T, Sasahira N, Kogure H, Hirano K, Tsujino T, Ijichi H, Tateishi K, Tada M, *et al*: Impact of S-1 in patients with gemcitabine-refractory pancreatic cancer in Japan. Jpn J Clin Oncol 40: 774-780, 2010.
13. Nakai Y1, Isayama H, Sasaki T, Sasahira N, Ito Y, Kogure H, Togawa O, Matsubara S, Arizumi T, Yagioka H, *et al*: Impact of S-1 on the survival of patients with advanced pancreatic cancer. Pancreas 39: 989-993, 2010.
14. Takasawa O, Fujita N, Noda Y, Kobayashi G, Ito K, Obana T, Horaguchi J, Koshita S, Kanno Y, Suzuki T, *et al*: Second-line treatment with S-1 in advanced pancreatic cancer. Gastroenterology 48: 207-213, 2009.
15. Kimura M, Morihata K, Ito D, Iwai M, Okada K, Usami E, Nakao T, Yoshimura T and Yasuda T: Continuous administration and safety of S-1 in adjuvant chemotherapy for gastric cancer. Cancer & chemotherapy 37: 829-834, 2010 (In Japanese).
16. Kimura M, Usami E, Yoshimura T, Yasuda T, Kaneoka Y, Teramachi H, Sugiyama T and Tsuchiya T: Pharmaceutical care for patients undergoing S-1 plus cisplatin therapy for unresectable recurrent gastric cancer. J Pharm Pract 26: 409-414, 2013.
17. Fridlender ZG and Albelda SM: Tumor-associated neutrophils: Friend or foe? Carcinogenesis 33: 949-955, 2012.
18. Todaka A, Fukutomi A, Boku N, Onozawa Y, Hironaka S, Yasui H, Yamazaki K, Taku K, Machida N, Sakamoto T and Tomita H: S-1 monotherapy as second-line treatment for advanced pancreatic cancer after gemcitabine failure. Jpn J Clin Oncol 40: 567-572, 2010.