Table 5. Treatment-emergent, all-causality adverse events reported by >20% of patients in any arm in any region

All grades/≥3 Grade, %	Overall study population		Japan		North America		European Union	
	Axitinib/ Gem (n = 305)	Placebo/ Gem (n = 308)	Axitinib/ Gem (n = 57)	Placebo/ Gem (n = 56)	Axitinib/ Gem (n = 75)	Placebo/ Gem (n = 81)	Axitinib/ Gem (n = 127)	Placebo/ Gem (n = 126)
Non-hematologic adverse events								
Nausea	47/4	37/3	58/2	46/5	45/8	36/2	41/4	37/1
Fatigue	42/9	37/7	70/9	46/9	49/13	53/11	26/6	25/5
Anorexia	37/6	27/4	68/16	52/4	33/5	21/5	24/4	22/3
Diarrhea	33/1	22/2	39/2	16/0	27/1	26/1	29/0	25/2
Vomiting	32/4	33/3	39/0	34/0	28/5	40/4	33/6	32/4
Constipation	29/1	31/2	49/0	41/4	24/3	38/4	21/0	22/1
Hypertension	28/7	9/2	44/12	4/2	31/7	14/5	23/5	10/0
Dysphonia	22/<1	4/0	60/2	18/0	17/0	2/0	10/0	0
Abdominal pain	21/7	19/6	7/2	4/0	24/9	25/10	24/8	22/5
Stomatitis	17/0	4/<1	46/0	2/0	12/0	2/1	8/0	6/0
Pyrexia	16/1	16/<1	23/0	20/0	12/1	23/0	18/2	11/1
Rash	14/1	14/1	21/0	32/2	8/1	16/1	13/1	7/1
Asthenia	14/5	13/2	0	0	12/11	12/2	23/6	21/3
Weight decreased	14/<1	10/<1	21/0	11/2	9/0	16/0	14/1	10/0
Alopecia	10/0	6/0	25/0	11/0	1/0	5/0	7/0	6/0
Dyspnea	9/2	8/3	0	7/2	20/7	12/5	8/0	8/3
Edema peripheral	8/0	16/1	2/0	11/2	13/0	33/0	6/0	9/0
Hand–foot syndrome	6/<1	1/0	25/2	2/0	0	0	2/0	1/0
Hematologic abnormalities								
Neutropenia[a]	24 /17	18/11	9/7	7/5	21/15	20/12	25/17	17/11
Thrombocytopenia[b]	16/5	12/3	0	0	27/9	21/7	11/2	13/2
Platelet count decreased[b]	14/4	13/4	51/14	38/13	11/4	14/4	2/0	4/0
Neutrophil count decreased[a]	10/7	13/9	42/32	50/39	8/3	7/5	1/1	4/2
Anemia[c]	9/1	18/3	0	0	12/3	27/5	10/0	23/2
White blood cell count decreased	7/1	5/1	30/4	21/7	1/1	1/0	1/1	0
Hemoglobin decreased[c]	6/1	9/2	21/2	23/2	7/3	11/2	0	4/1

Gem, gemcitabine

[a]Using terminology of neutropenia or neutrophil count decreased was based on physician's discretion.

[b]Using terminology of thrombocytopenia or platelet count decreased was based on physician's discretion.

[c]Using terminology of anemia or hemoglobin decreased was based on physician's discretion.

In Japanese patients, axitinib/gemcitabine treatment was associated with higher (>20%) incidence of all-causality fatigue, diarrhea, hypertension, dysphonia, stomatitis and hand–foot syndrome than with placebo/gemcitabine treatment. In addition, hypothyroidism and proteinuria were more common in Japanese patients treated with axitinib/gemcitabine compared with placebo/gemcitabine (hypothyroidism: 8.8 vs. 1.8%; proteinuria: 15.8 vs. 5.4%), but the majority were Grades 1–2.

AEs that led to discontinuation of axitinib treatment in Japanese patients were fatigue, general physical health deterioration, pneumonia, anorexia, neoplasm progression, gastrointestinal perforation and intestinal fistula (one patient [1.8%] each). General disorders (8.0%), including asthenia (4.0%), gastrointestinal disorders (4.0%) and psychiatric disorders (2.7%), were the reasons for axitinib treatment discontinuation in patients in North America, and general disorders (3.9%), including disease progression (2.4%), and hepatobiliary disorders (2.4%), among patients in the European Union.

Exploratory analysis for relationship between OS and hypertension

The results indicated that there were no notable differences in OS between axitinib/gemcitabine-treated patients who experienced hypertension (maximum diastolic BP ≥90 mm Hg) during Cycle 1 compared with those who did not develop hypertension in the overall study population, in North America or the European Union (Fig. 2A, C and D). Among Japanese patients treated with axitinib/gemcitabine, OS seemed to be slightly longer in those who experienced hypertension than those who did not (Fig. 2B). However, it is unlikely of clinical significance since it was similar to that in placebo/gemcitabine-treated Japanese patients who did not experience hypertension.

Discussion

The current analysis by region (Japan, North America and the European Union) of the Phase III trial of axitinib in combination with gemcitabine in patients with advanced pancreatic cancer revealed several findings. First, a combination treatment of axitinib and gemcitabine did not improve OS over gemcitabine alone in Japanese patients with advanced pancreatic cancer, which is consistent with results reported in the overall study population (9). Similarly, no survival benefit of adding axitinib to gemcitabine was observed in patients in North America or in the European Union. Second, although the previous Phase II open-label randomized study suggested greater survival benefit of axitinib/gemcitabine in patients with locally advanced than metastatic pancreatic cancer (8), this Phase III study failed to confirm better

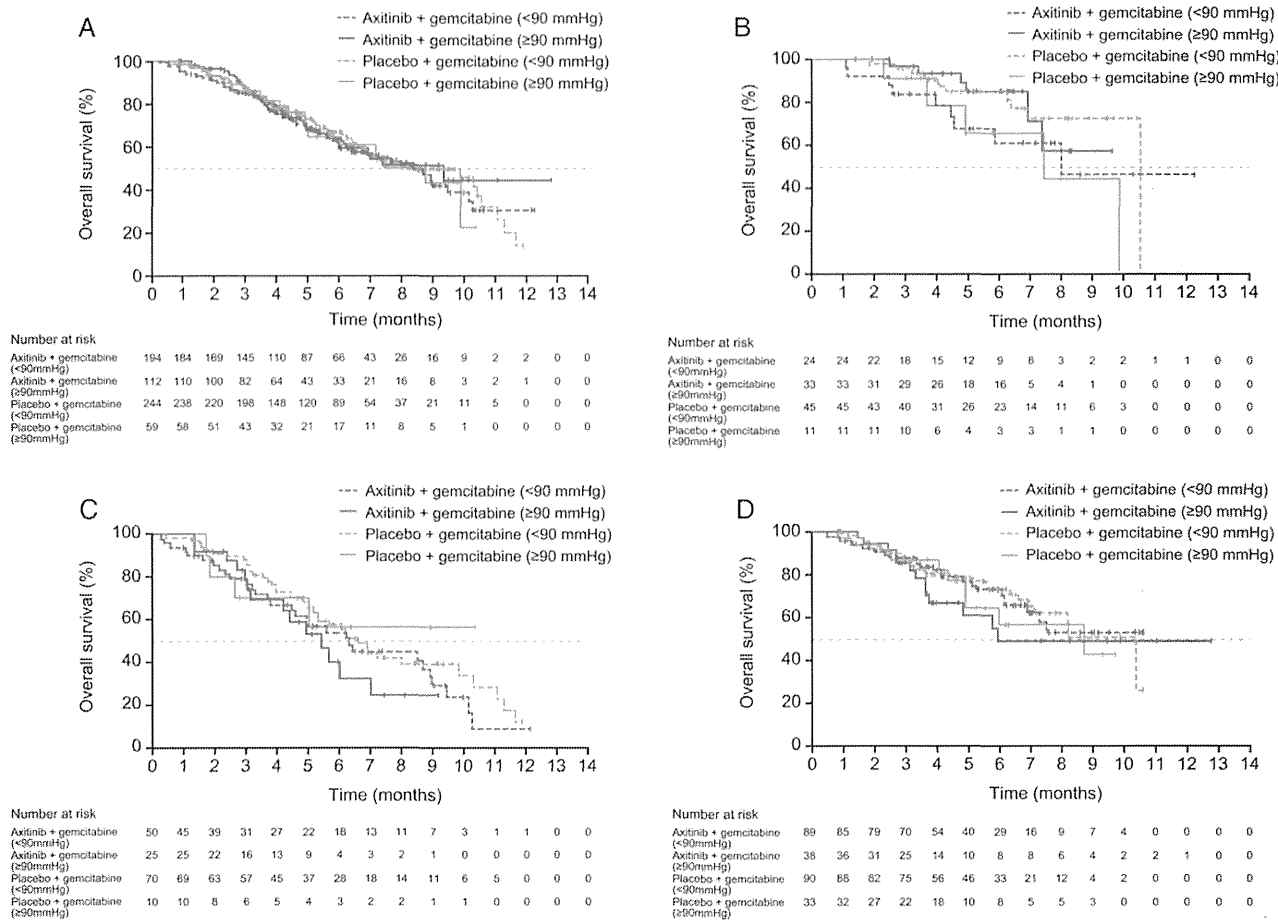

Figure 2. Kaplan–Meier estimates for overall survival by maximum diastolic blood pressure during Cycle 1 for axitinib/gemcitabine vs. placebo/gemcitabine in the overall study population (**A**), and in patients in Japan (**B**), North America (**C**) and the European Union (**D**).

survival in patients with locally advanced disease in any of the three regions. Third, no difference was found for PFS between the two treatment arms in each region. Although the use of follow-up systemic treatment ranged between 9.1% and 22.2% in the three regions, interpretation of such data to determine their impact on OS would be complicated, given that many of the patients were still on study treatment at the time of the final analysis. It is noteworthy that HR for OS was close to 2 for locally advanced disease and ~1 for metastatic disease in each region. These results suggested that patients with locally advanced and those with metastatic disease might not respond to study treatment in the same way and thus should be evaluated separately in a clinical study, as has been done in some other Phase III studies (10,11).

Although the lack of efficacy with the combination therapy was consistent across the three regions evaluated, we observed some geographic differences in clinical practice as well as baseline characteristics of patients enrolled in the study. Patients in Japan received gemcitabine treatment for the longest duration (5 and 4 cycles started and 119 and 99 days on gemcitabine treatment in the axitinib/gemcitabine and placebo/gemcitabine arms, respectively) and those in North America were the shortest (2 and 3 cycles started and 43 and 71 days, respectively). Generally, longer treatment duration as observed with gemcitabine in Japanese patients in this study may contribute to the better efficacy. The majority of patients in Japan (78 and 77% in the axitinib/gemcitabine vs. placebo/gemcitabine arm, respectively) had ECOG PS 0, in contrast to 38% of patients in either arm in North America. The percentage of patients who had locally advanced rather than metastatic disease was highest in Japan (31 and 34% in the axitinib/gemcitabine vs. placebo/gemcitabine arm, respectively) and lowest in North America (20% in either arm), which might have impacted treatment duration. During treatment, the percentage of Japanese patients with axitinib dose reduction or dose interruption was higher than that in the other two regions, and conversely, a lower percentage of Japanese patients had axitinib dose increase. It is noteworthy that axitinib plasma exposures were similar between Japanese and Caucasian subjects (12,13). Thus, axitinib pharmacokinetics does not seem to account for the higher rate of axitinib dose decrease or the lower rate of axitinib dose increase in Japanese patients. The higher percentage of patients with dose reduction for gemcitabine or axitinib in Japan than in the other two regions could be partly explained by the fact that Japanese patients were on treatment longer, and thus, had more opportunities for dose reduction.

Common AEs experienced by Japanese patients treated with placebo/gemcitabine in this study included anorexia, fatigue and gastrointestinal and hematologic toxicities, which were similar to those reported previously in Japanese patients with advanced pancreatic cancer treated with gemcitabine (14–16). Addition of axitinib to gemcitabine was associated with ≥20% increase in the incidence of dysphonia, stomatitis, hypertension, fatigue, diarrhea and hand–foot syndrome in Japanese patients, but not among patients in North America or the European Union. Decreased platelet counts, neutrophil counts, white blood cell counts and hemoglobin levels were more frequently reported by Japanese patients treated with either axitinib/

gemcitabine or placebo/gemcitabine compared with patients in North America or the European Union. On the other hand, neutropenia, thrombocytopenia and anemia were more common in patients in North America and the European Union. In light of the fact that axitinib plasma exposures were similar between Japanese and Caucasian (12,13), it is unclear whether differences in some AEs between Japanese patients and patients from the other two regions indicate pharmacogenomic differences. Additionally, the use of different terminologies (e.g. 'neutropenia' vs. 'decreased neutrophil count') by the investigators in different regions might have led to some extent to the different incidence rates of hematologic toxicities. Although there were some notable differences in the incidence of some AEs, the current analysis showed that the safety profile of axitinib in Japanese patients was generally comparable to that observed in patients in North America or the European Union.

Hypertension is a known AE associated with axitinib treatment, and a correlation between BP and efficacy outcome has been shown in axitinib-treated patients with advanced renal cell carcinoma (13,17). An exploratory analysis of data from the Phase II study of axitinib/gemcitabine suggested a possible association between hypertension and OS in advanced pancreatic cancer (8). However, the current analysis did not reveal any significant relationship.

The limitation of the current analyses is that follow-up period in this Phase III study was short, and consequently, there were few events that had occurred before the study was terminated. Hence, OS did not mature at the time of the interim analysis. The lack of efficacy for the combination therapy seen here, however, is in line with disappointing results reported in other randomized Phase III studies of gemcitabine in combination with two other antiangiogenic agents, bevacizumab or sorafenib (18–20). These results suggest antiangiogenic agents, including axitinib, do not appear to enhance the survival of patients with advanced pancreatic cancer when combined with gemcitabine. Hence, novel agents with different mode of action and/or new approaches are needed to improve survival in these patients.

In conclusion, the addition of axitinib to gemcitabine did not improve OS in patients with advanced pancreatic cancer in Japan, North America or the European Union. Although incidence rates for some AEs differed between patients in Japan and those in the other regions, the nature of common AEs and overall safety profile were generally similar.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org

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Conflict of interest statement

Tatsuya Ioka has management/advisory affiliation with Chugai Pharmaceutical. Takuji Okusaka received speaker honoraria and research funding from Pfizer. Shinichi Ohkawa, Narikazu Boku and Akira Sawaki have no conflict of interest to disclose. Yosuke Fujii, Yoichi Kamei, and Satori Takahashi are employed by Pfizer Japan. Katsushi Namazu and Yoshiko Umeyama are employed by Pfizer Japan and own stock in Pfizer. Paul Bycott is employed by and owns stock in Pfizer. Junji Furuse received consulting fees from Chugai Pharmaceutical, Taiho Pharmaceutical, Eli Lilly Japan, Pfizer, Bayer Pharmaceutical, and Zeria Pharmaceutical.

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〔特　　集〕膵癌化学療法の新たな展開

特集にあたって

古瀬　純司*

要　旨：膵癌切除手術の補助療法として，ゲムシタビンに続いてS-1による術後補助療法が確立し，大きく治療成績が改善している．最近では術前補助療法としてゲムシタビン＋S-1併用療法やFOLFIRINOX療法などの抗腫瘍効果の高い治療を用いた臨床試験が進められている．切除不能膵癌の化学療法では，フランスからFOLFIRINOX療法が報告され，標準治療のゲムシタビンに比べ大きな生存期間の延長が得られている．日本でも第II相試験が実施され，2013年，適応が承認された．このような化学療法の進歩を実臨床に確実に導入し，実施する目的で膵癌診療ガイドラインが作成されている．今回の特集は切除手術の術前，術後補助療法と新たに登場したFOLFIRINOX療法を取り上げ，最新の膵癌診療ガイドラインから膵癌の化学療法を展望するという内容で企画された．膵癌化学療法に対する理解が進むものと期待される．

索引用語：膵癌　化学療法　補助療法　FOLFIRINOX療法　膵癌診療ガイドライン

日本の国民にとって「がん」は最も死を意識する疾患であり，毎年36万人以上の方が「がん」で亡くなっている．中でも膵癌は極めて予後不良な疾患であり，がん統計では，2014年の膵癌罹患数は37,700人，死亡数は31,900人と予測されている[1]．がんの予防や早期診断，さらに様々な治療法が着実に進む中で，膵癌は罹患数と死亡数がほぼ同じであり，なおかつ増え続けている．

がんの治療は，早期診断，早期治療，そして確実に切除することが基本である．膵癌でも外科切除への期待から，多少の犠牲を払っても広く確実に病巣を切除することが治癒につながるとして，多くの努力が進められてきた．しかし，膵癌の切除に伴うリンパ節郭清について標準郭清と拡大郭清では差がないことが示され[2]，患者のQOLの維持という方向に変わってきたように思われる．一方，有望な薬剤の登場に伴い切除後の予後改善に化学療法に対する期待が大きくなった．切除不能膵癌に対する標準治療薬となったゲムシタビンを用いた術後補助療法により死亡のリスクは24%減少した(ハザード比0.76)[3]．さらに，わが国から報告されたS-1による術後補助療法ではゲムシタビンに対するS-1のハザード比は0.54と死亡のリスクのほぼ半減を達成している[4]．切除手術において化学療法は大きく貢献しているといえる．最近ではより強力な化学療法を先に用いるという術前補助療法に注目が移ってきている．ゲムシタビン＋S-1やFOLFIRINOXなどの抗腫瘍効果の高い化学療法が登場し，術前の全身状態が良好な状態で病勢を抑え込む，というコンセプトである．

切除不能膵癌の化学療法もこの2～3年，大きく変わってきている．1990年代後半，切除不能膵癌に対するゲムシタビンと5-FUによる第III相試験の結果[5]，ゲムシタビンが初めて膵癌の標準治療薬として確立し，膵癌の薬物療法の大きな第一歩となった．それ以降，様々な新しい薬剤や併用療法が次々と試みられたが，確実にゲムシタビン単独治療を超える治療はほとんどなかった．そのような中で，2010年，フランスからFOLFIRINOX療法の第III相試験の結果が報告され，標準治療のゲムシタビンに比べ，FOLFIRINOXで奏効割合，無増悪生存期間，全生存期間のいずれも大き

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な改善が得られている[6]．FOLFIRINOXはフルオロウラシル，レボホリナート，イリノテカン，オキサリプラチンの4剤を併用する治療であり，わが国ではフルオロウラシルを除いて保険適用が認められていなかった．本治療の導入は至急の課題であり，日本人での安全性と有効性を確認する第II相試験が治験として実施された[7]．FOLFIRINOX療法は公知申請，早期審査，早期承認と企業，学会，研究者，規制当局の努力と協力でそれ程遅れずに2013年，日本でも適応が認められた．

予後不良の膵癌も，化学療法の進歩を中心に少しずつでも確実に改善しつつある．遠隔転移を有する膵癌患者の生存期間中央値は，1990年代の4〜5ヵ月が今11ヵ月を超えてきている．このような化学療法の進歩を実臨床に確実に導入し，実施するということも重要なポイントである．その観点から，日本膵臓学会が主体となって作成されている膵癌診療ガイドラインの役割は大きい．2006年に膵癌診療ガイドラインが初めて出された後，2009年版，2013年版と改訂され，2014年7月には化学療法の項が一部改訂された．初版ではゲムシタビンのみであった推奨レジメンが2013年にはゲムシタビン単剤，ゲムシタビン＋エルロチニブ併用，S-1単剤と3つに増え，さらに2014年の一部改訂ではFOLFIRINOXが追加された．ガイドラインには実施可能な治療を遅れることなく出していく役割が求められている．さらにはエビデンスのある治療をタイムリーに載せることで実臨床への導入を促進するという役割も期待されてきている．

今回の特集は切除手術の術前，術後補助療法と新たに登場したFOLFIRINOX療法を取り上げ，最新の膵癌診療ガイドラインから膵癌の化学療法を展望するという内容で企画された．膵癌化学療法の現状と役割，さらに今後の展望に対する理解が進むものと期待される．

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Prognostic value of neutrophil–lymphocyte ratio and level of C-reactive protein in a large cohort of pancreatic cancer patients: a retrospective study in a single institute in Japan

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Abstract

Objective: Recent studies suggest that systemic inflammatory response is closely associated with cancer patient prognosis. Although several inflammatory prognostic markers have been proposed, the data to support their validity are lacking in large Japanese cohorts.

Methods: This is a retrospective study to examine the prognostic value of inflammatory markers, such as C-reactive protein, neutrophil–lymphocyte ratio, platelet–lymphocyte ratio and modified Glasgow prognostic scale, in pancreatic cancer. Selection criteria were admittance to hospital between January 2008 and December 2012, histologically confirmed adenocarcinoma, diagnosis of invasive ductal pancreatic cancer compatible by computed tomography imaging, and followed-up until death or for 180 days or longer. The primary end point was overall survival, which was measured from the day of histological diagnosis.

Results: There were 440 patients who met the selection criteria. Of the 440 cases, 200 (45.5%) received curative resection (166 Stage I/II and 34 Stage III patients), 237 (53.9%) received chemotherapy (4 Stage I/II, 92 Stage III and 141 Stage IV patients), and the remaining 3 received palliative care. Univariate and multivariate regression analyses revealed that advanced computed tomography stage, high level of C-reactive protein (0.45 mg/dl or greater), neutrophil–lymphocyte ratio (2.0 or greater) and CA19-9 level (1000 U/ml or greater) were significantly associated with worse prognosis.

Conclusions: We verified the results of previous studies, and showed that neutrophil–lymphocyte ratio and C-reactive protein also had prognostic value in a large Japanese PC cohort.

Key words: NLR, CRP, mGPS, PLR, survival

Introduction

Pancreatic cancer (PC) has become the fifth most common cause of cancer-related mortality in Japan; it has been estimated that PC was responsible for 29 916 deaths in 2012 (1), representing ~8% of all cancer deaths. Despite recent improvements in diagnostic techniques, only a small proportion of patients are eligible for surgery, even though resection represents the only curative treatment available thus far. Accordingly, the prognosis of PC patients is extremely poor, with a 5-year survival rate after diagnosis of <5% (2).

Recent studies suggest that the systemic inflammatory response is closely associated with cancer patient prognosis (3,4). Several parameters of the systemic inflammatory response, including level of C-reactive protein (CRP), neutrophil–lymphocyte ratio (NLR), derived NLR (dNLR), platelet–lymphocyte ratio (PLR) and modified Glasgow prognostic score (mGPS), have been demonstrated in numerous reports as good prognostic indicators in lung cancer (5), hepatocellular carcinoma (6), melanoma (7), renal cell carcinoma (8), gastric cancer (9) and colorectal cancer (10). Moreover, some studies have shown that these parameters can predicted clinical outcome in regardless of the primary site (11,12).

Further, initial reports have already indicated that the inflammatory response is predictive of prognosis in patients with PC, but most of these studies included only relatively small number of cases (13–17). An Austrian group has reported the prognostic value of NLR, dNLR and CRP as useful inflammatory markers in their large cohort of PC patients (18–20). In the present study, we aimed to validate the prognostic significance of inflammatory markers in a large cohort of Japanese PC patients with reference to the Austrian studies.

Patients and Methods

This retrospective study included data from 493 consecutive patients who were diagnosed with PC at the Gastroenterology Center, Cancer Institute Hospital of Japanese Foundation for Cancer Research between January 2008 and December 2012. Among these 493 patients, we selected those for the current study if all of the following criteria were met: (i) histologically or cytologically confirmed adenocarcinoma, (ii) invasive ductal PC compatible by computed tomography (CT) imaging and (iii) followed-up until death or for 180 days or longer.

Clinical variables collected in this study were: age, gender, height, weight and performance status (PS) according to the Eastern Cooperative Oncology Group grading system; white blood cell (WBC) count; fraction of neutrophil and lymphocyte in WBC differentiation (%); levels of albumin, bilirubin, CRP and carbohydrate antigen 19-9 (CA19-9); location of the primary pancreatic tumor; clinical CT stage according to the seventh edition of TNM classification; type of therapy (i.e. tumor resection, chemotherapy or symptomatic treatment); date of surgical intervention or biopsy and date of the final follow-up or death. The baseline data were obtained within 30 days prior to surgical intervention or biopsy.

The relationship between each baseline variable and long-term survival was investigated by univariate and multivariate analyses, with special focus on the prognostic impact of systemic inflammation markers. On the basis of previous studies, CRP level of 0.45 mg/dl, NLR of 2.0, dNLR (absolute count of neutrophils divided by the absolute WBC count minus the absolute count of neutrophils) of 2.3 and PLR of 150 were selected as cutoff values for validation. The mGPS was applied by combining CRP and albumin levels: 0 was defined as normal values of CRP and albumin; 1 was defined as increased CRP (1.0 mg/dl or greater) and normal albumin; and 2 was defined as increased CRP and decreased albumin (<3.5 g/ml). Other than the five inflammatory markers, variables included in the prognostic analysis were: age (65 years or younger versus older than 65); gender; PS (0 versus 1); body mass index (>25 versus 25 or greater); location of the primary tumor (head versus body–tail); clinical CT Stage (I/II, III or IV); and CA 19-9 (>1000 U/ml versus 1000 U/ml or greater).

The primary end point of this study was overall survival (OS), defined as the time from the date of histological confirmation (the date of surgery or biopsy) to death due to any cause or to the last known date alive. All patients were assessed in December 2013. Kaplan–Meier survival plots were generated, and differences in survival among subgroups classified by each factor were evaluated by log-rank tests. Cox regression was used to determine univariate hazard ratios for OS. Age, PS and all variables with significant prognostic value in the univariate analysis were selected for further evaluation in the final multivariate Cox proportional hazard model. Multivariate Cox proportion analysis by backward elimination method was performed to determine the influence of the different variables on OS. Hazard ratios estimated by the Cox analysis were reported as relative risks with corresponding 95% confidence intervals. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the PASW Statistics 18 program (SPSS Inc., Chicago, IL, USA).

The Institutional Review Board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research approved this study, and waived the need for written informed consent from the participants because this was a retrospective non-intervention study.

Results

Of the 493 patients, 440 met the selection criteria. Of the remaining 53, 28 had other tumor histologies including neuroendocrine tumor, and 25 were transferred to a community hospital to receive palliative care within 6 months after diagnosis. Patient characteristics are summarized in Table 1. Of the 170 patients diagnosed with Stage I/II potentially resectable disease, 4 received chemotherapy because micro-metastases were found by laparotomy. Of the 127 patients diagnosed with Stage III disease, 34 underwent resection of the pancreas, 92 received chemotherapy and the remaining 1 received symptomatic treatment. Of the 143 patients diagnosed with Stage IV disease, 141 received chemotherapy and the remaining 2 received symptomatic treatment. Consequently, 200 (45.5%) patients received curative resection (166 Stage I/II and 34 Stage III cases), 237 (53.9%) received chemotherapy (4 Stage I/II, 92 Stage III and 141 Stage IV patients) and the remaining 3 received palliative care. Of the 440 selected patients, 313 (71.1%) died and the remaining 127 were still alive at the time of analysis. The median follow-up time of the 127 survivors was 18.7 months, ranging from 6.1 to 68.2 months. The median survival time of patients from the whole cohort was 11.6 months (interquartile range: 7.1–20.1 months).

Univariate Cox regression revealed that advanced CT stage, pancreatic body–tail cancer, high level of CRP, NLR, dNLR and CA19-9 level were significantly associated with worse prognosis (Table 2). We continued to analyze NLR but not dNLR in the multivariate analysis because the hazard ratio of NLR was higher than that of dNLR (1.894 versus 1.576, respectively). PLR and mGPS did not show any evident prognostic impact on survival in our cohort. In the multivariate analysis, CT stage, level of CRP, NLR and CA19-9 level were identified as independent prognostic factors in our cohort (Table 3).

Figure 1 demonstrates OS curves stratified by NLR in each CT stage, respectively. The number of patients with NLR >2.0 and those with NLR ≥2.0 were 71 (41.8%) and 99 (58.2%) in Stage I/II, 48 (37.8%) and 79 (62.2%) in Stage III and 21 (14.7%) and 122 (85.3%) in Stage IV. The prognostic value of NLR was clear especially in CT Stage I/II disease ($P = 0.014$, log-rank test). But there was no significant difference between Stages III and IV ($P = 0.079$ and $P = 0.125$).

Figure 2 demonstrates OS curves stratified by CRP in each CT stage, respectively. The number of patients with CRP <0.45 and

Table 1. Patient characteristics

Age (years)		
Median (range)	67	32–88
65 or younger	179	40.7%
Older than 65	261	59.3%
Gender		
Male	249	56.6%
Female	191	43.4%
Performance status		
0	378	83.3%
1	62	13.7%
Body mass index		
Median (range)	21.6	13.0–33.8
<25	375	85.2%
25 or greater	65	14.8%
Location of the primary tumor		
Head	220	50.0%
Body–tail	220	50.0%
Clinical CT stage		
I/II	170	38.6%
III	127	28.9%
IV	143	32.5%
C-reactive protein (mg/dl)		
Median (range)	0.12	0.01–21.9
<0.45	321	73.0%
0.45 or greater	119	27.0%
Neutrophil–lymphocyte ratio		
Median (range)	2.47	0.7–27.7
<2	140	31.8%
2 or greater	300	68.2%
Derived neutrophil–lymphocyte ratio		
Median (range)	1.77	0.5–13.3
<2.3	324	73.6%
2.3 or greater	116	26.4%
Platelet–lymphocyte ratio		
Median (range)	140.0	40.4–930.8
<150	239	54.3%
150 or greater	201	45.7%
Modified Glasgow prognostic score		
0	367	83.4%
1	49	11.1%
2	24	5.5%
Albumin (g/dl)		
Median (range)	4.0	2.4–5.0
<3.5	48	10.9%
3.5 or greater	392	89.1%
CA19-9 (U/ml)		
Median (range)	436.2	2.0–50 000
<1000	275	625%
1000 or greater	165	37.5%

those with CRP ≥0.45 were 147 (86.5%) and 23 (13.5%) in Stage I/II, 102 (80.3%) and 25 (19.7%) in Stage III and 72 (50.3%) and 71 (49.7%) in Stage IV, respectively. The prognostic value of CRP was evident in CT Stage III and IV disease ($P = 0.015$ and $P < 0.001$).

Figure 3 shows box plots of CRP and NLR in each CT stage. The dotted line means the cutoff level. The fraction of patients with NLR under the cutoff level was small especially in Stage IV, whereas most patients in Stage I/II had lower CRP level than the cutoff level.

Figure 4 demonstrates plots of the cumulative distribution function of NLR and CRP. The degree of asymmetric distribution of CRP was larger than that of NLR, with skewness coefficients of 5.568 and 4.803, respectively.

Table 2. Univariate cox regression

	HR	95% CI	*P* value
Age			
65 or younger	1		
Older than 65	0.806	0.644–1.008	0.059
Gender			
Male	0.985	0.788–1.232	0.897
Female	1		
Performance status			
0	1		
1	1.261	0.924–1.720	0.143
Body mass index			
<25	1		
25 or greater	1.192	0.883–1.609	0.252
Location of the primary tumor			
Head	1		
Body–tail	1.499	1.199–1.873	<0.001
Clinical CT stage			
I/II	1		
III	2.225	1.666–2.972	<0.001
IV	5.351	3.996–7.166	<0.001
C-reactive protein (mg/dl)			
1			
0.45 or greater	2.323	1.820–2.966	<0.001
Neutrophil–lymphocyte ratio			
<2.0	1		
2.0 or greater	1.894	1.474–2.435	<0.001
Derived neutrophil–lymphocyte ratio			
<2.3	1		
2.3 or greater	1.576	1.234–2.012	<0.001
Platelet–lymphocyte ratio			
<150	1		
150 or greater	1.048	0.838–1.309	0.683
Modified Glasgow prognostic score			
0	1		
1	2.61	1.89–3.605	<0.001
2	1.465	0.906–2.369	0.119
Albumin (g/dl)			
<3.5	1		
3.5 or greater	1.161	0.801–1.683	0.431
CA19-9 (U/ml)			
<1000	1		
1000 or greater	2.002	1.591–2.519	<0.001

HR, hazard ratio; CI, confidence interval.

Discussion

Previous studies suggest that disease progression in cancer patients is not only driven by the intrinsic properties of tumor cells, but also by systemic host reactions. Some systemic factors, in the shape of cytokines and other chemical messengers, may play an important role in cellular proliferation and metastatic ability (3,4). Although the detailed mechanisms have not been fully elucidated yet, several markers that reflect systemic inflammation have been reported to be closely associated with patient prognosis in different types of cancer (5–12). Among these inflammatory factors, we tested level of CRP, NLR, dNLR, PLR and mGPS in a large Japanese PC cohort in the current study. An Austrian group had already reported that NLR (18), dNLR (19) and CRP (20) predicted clinical outcome, and our study aimed to validate their findings. As a result, we confirmed that NLR and CRP have prognostic value in a large Japanese cohort similar to the Austrian studies. On the other hand, PLR and mGPS did not

Table 3. Multivariate cox regression

	HR	95% CI	*P* value
Age			
65 or younger	1		
Older than 65	0.834	0.665–1.045	0.115
Performance status			
0	1		
1	1.284	0.923–1.788	0.138
Location of the primary tumor			
Head	1		
Body–tail	1.07	0.842–1.359	0.582
Clinical CT stage			
I/II	1		
III	2.191	1.638–2.931	<0.001
IV	4.141	3.035–5.648	<0.001
C-reactive protein (mg/dl)			
<0.45	1		
0.45 or greater	1.695	1.308–2.197	<0.001
Neutrophil–lymphocyte ratio			
<2.0	1		
2.0 or greater	1.404	1.078–1.830	0.012
CA19-9 (U/ml)			
<1000	1		
1000 or greater	1.435	1.127–1.826	0.003

demonstrate any prognostic value in our cohort, possibly due to ethnic difference and/or specificity of cancer type.

As compared with the Austrian cohort, there were more patients with earlier stage disease in our cohort. The fraction of Stage IV patients was 70% in the Austrian studies and 33% in this report. The mean values of NLR and CRP were 4.75 and 2.32 mg/dl, respectively, in the Austrian reports, and 3.06 and 0.80 mg/dl, respectively, in the current one. The median survival time and interquartile range were 7 and 3–17 months, respectively, in the Austrian cohort, and 11.6 and 7.1–20.1 months, respectively, in ours. Due to a high surgeon volume in our institute, we fortunately had an advantage in recruiting many PC patients with earlier stage. In any case, the important fact was that the prognostic impacts of NLR and CRP were confirmed in resectable and unresectable PC patients, respectively, in both European and Asian cohorts.

Although we verified the prognostic value of NLR and CRP in PC patients, there were differences between the characters of NLR and CRP as prognostic markers. One important point is that NLR is a relative value. Because a neutrophil count of zero is not a realistic situation, thus, NLR cannot approach zero (Fig. 4). Figure 3 shows the distribution of NLR and CRP in each clinical stage. The level of NLR tended to become higher as the clinical stage progressed. Accordingly, the cutoff level of 2.0 was appropriate for resectable disease but

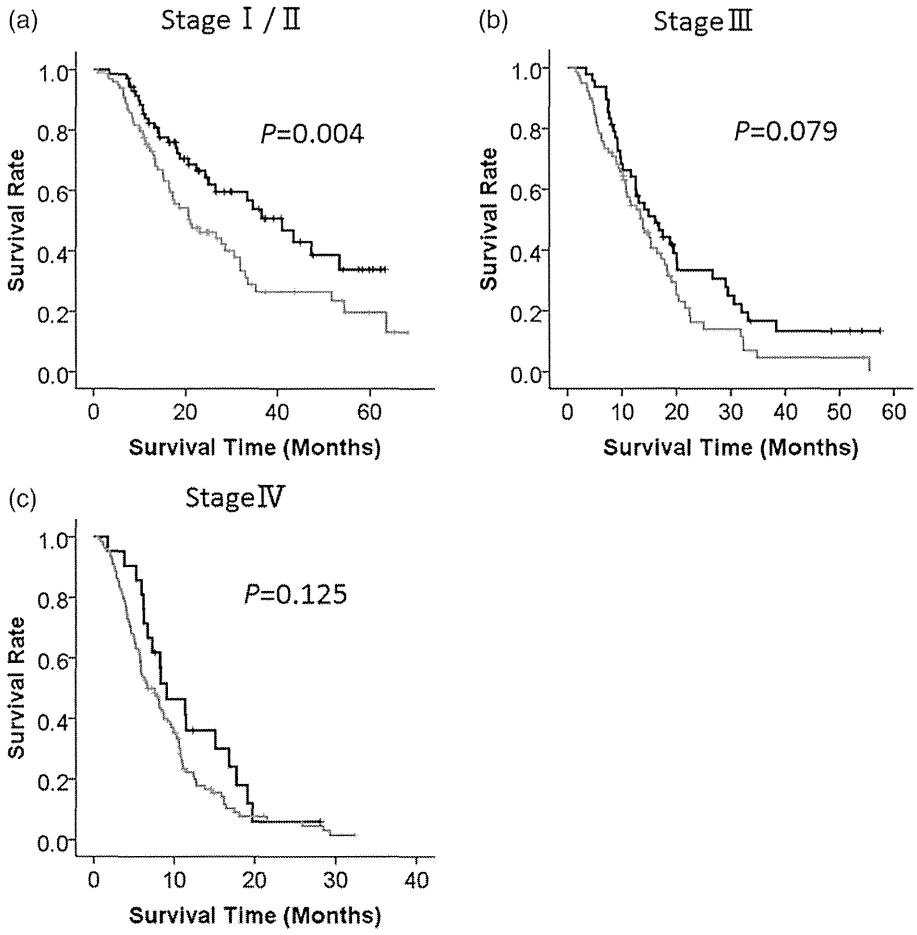

Figure 1. Overall survival curves stratified by neutrophil–lymphocyte ratio (NLR) for Stage I/II (a), Stage III (b) and Stage IV (c). Vertical lines represent censoring of data. Black and gray lines indicate subgroup of patients with NLR <2.0 and those with NLR ≥2.0, respectively. Prognosis of patients with increased NLR was significantly poorer in Stage I/II ($P = 0.004$, log-rank test).

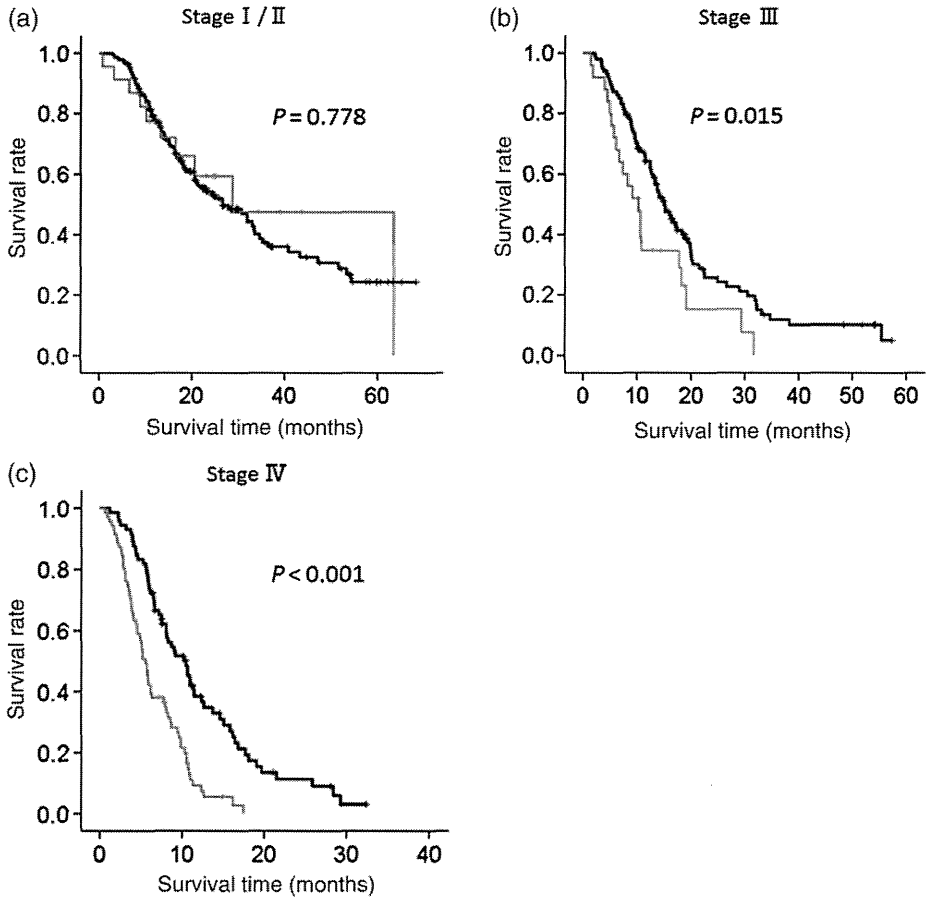

Figure 2. Overall survival curves stratified by C-reactive protein (CRP) for Stage I/II (a), Stage III (b) and Stage IV (c). Vertical lines represent censoring of data. Black and gray lines indicate subgroup of patients with CRP <0.45 and those with CRP ≥0.45, respectively. Prognosis of patients with increased CRP was significantly poorer in Stage III ($P = 0.015$) and Stage IV ($P < 0.001$, log-rank test).

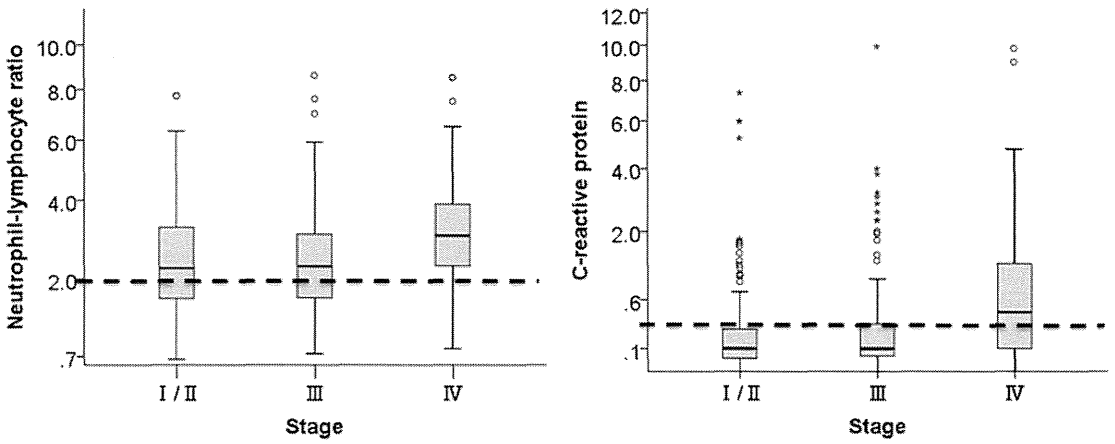

Figure 3. Box plots of CRP and NLR stratified by clinical stage. The dotted line denotes the cutoff level. The fraction of patients with NLR under the cutoff level was small especially in Stage IV, whereas most patients in Stage I/II had lower CRP level than the cutoff level.

it was too low to show the statistical significance in unresectable disease. If the cutoff level of NLR was set separately in each clinical stage, the prognostic value of NLR would be evident in both resectable and unresectable diseases. In practice, when we applied the cutoff level of 5.0 for NLR, the result was opposite from the result mentioned above, namely, the prognostic value of NLR was evident in unresectable disease, but not evident in resectable disease. On the other hand, CRP level is an absolute value, and small values close to zero represent a normal condition in general. To determine the cutoff level of CRP for patients especially in early stage was difficult because almost all

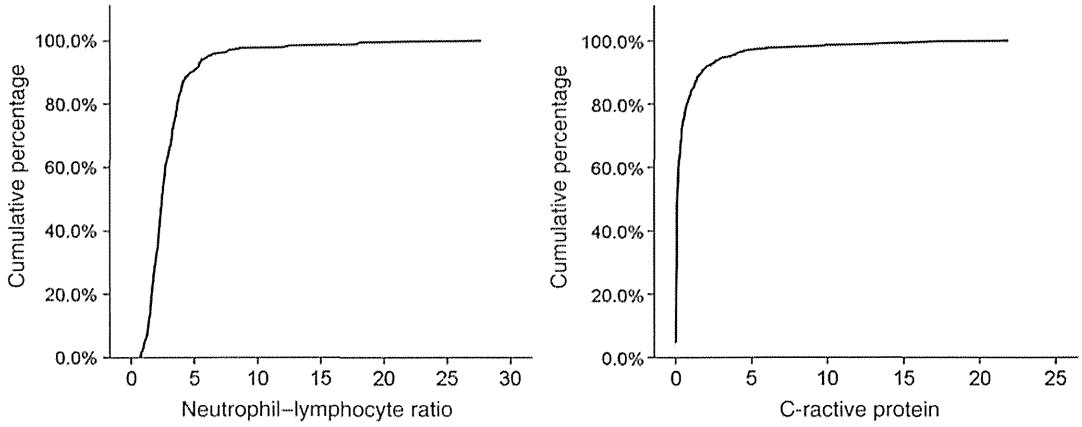

Figure 4. Cumulative distribution function plots of NLR and CRP. NLR cannot approach zero (95% of the NLR in our cohort were distributed between 1.1 and 6.2). On the contrary, small CRP values close to zero represent a normal condition. In the present study, 74% of the CRP levels were <0.5 mg/dl.

of the patients had a normal CRP level. For that reason, the prognostic value of CRP was relatively clear for advanced disease.

In conclusion, we verified the results of the Austrian studies, and revealed the prognostic value of NLR and CRP in a large PC cohort. We also found that the cutoff value of 2.0 for NLR clearly demonstrated prognostic value in potentially resectable disease, whereas CRP was a useful prognostic factor in patients who are not good candidates for curative resection. Further investigations to clarify the optimal NLR and CRP cutoff levels are warranted.

Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Improved survival with combined gemcitabine and S-1 for locally advanced pancreatic cancer: pooled analysis of three randomized studies

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Abstract

Background The long-term prognosis for localized pancreatic cancer (PC) remains poor. Three randomized trials (GEST phase III, JACCRO PC-01 phase II and GEMSAP phase II) evaluated gemcitabine (Gem) with or without S-1 for patients with metastatic and locally advanced PC. A pooled analysis based on published data examined whether Gem with S-1 (GS) is superior to Gem alone in overall survival (OS) in patients with locally advanced PC.

Methods Data were extracted on 193 patients: 31 (JACCRO), 28 (GEMSAP), and 134 (GEST). OS was used for primary endpoint and progression-free survival (PFS) was used for secondary endpoint. A general variance-based method was used to estimate the pooled HR and 95% CI between GS (n = 96) and Gem (n = 97).

Results Meta-analysis demonstrated that the overall risk of death was significantly different between the two chemotherapies (hazard ratio = 0.673, 95% confidence interval: 0.488–0.929, P = 0.016). The median PFSs for GS and GEM in the JACCRO, GEMSAP, and GEST studies were 12.0, 12.6, and 10.7 months, and 4.1, 8.1, and 6.2 months, respectively (P = 0.001). The random-effect pooled estimate for 165 patients showed the objective response rate (ORR) in the GS group (28.4%) was better in the Gem group (8.3%, P = 0.001).

Conclusions GS improved ORR, PFS and OS in patients with locally advanced PC over Gem alone. GS could become one of the front-line chemotherapeutic agents.

Keywords Gemcitabine with S-1 · Locally advanced pancreatic cancer · Pooled analysis

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Introduction

Pancreatic cancer (PC) is currently the eighth leading cause of cancer-related mortality worldwide, with an estimated

266,000 deaths in 2008 [1]. At the time of diagnosis, approximately half of patients have metastases, and median survival does not exceed 6 months. Thus, only a small proportion of patients are eligible for surgery at diagnosis, and there is a strong requirement for active systemic treatments for this cancer. Gemcitabine (Gem) is the standard treatment for advanced PC, offering better overall survival (OS) than fluorouracil [2]. Although various Gem-based combination regimens have been evaluated, erlotinib or nab-paclitaxcel added to Gem showed a survival benefit over Gem [3, 4]. Fluorouracil/leucovorin plus irinotecan and oxaliplatin (FOLFIRINOX), a Gem-free combination regimen, has recently demonstrated a clear survival benefit over Gem for patients with metastatic PC who have a performance status of 0–1 [5]. However, because FOLFIRINOX is associated with significant toxicity, this regimen requires close monitoring and must be limited to patients with good performance status [6].

S-1 is a new oral fluoropyrimidine derivative in which tegafur is combined with 2 5-chloro-2,4-dihydroxypyridine modulators and oteracil potassium, a potentiator of 5-fluorouracil's (5-FU's) antitumor activity that also decreases gastrointestinal toxicity. In Japan, clinical trials of S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) have been conducted since the early 2000s for patients with PC. Combination chemotherapy with gemcitabine and S-1 is reportedly well tolerated and active against advanced pancreatic cancer [7–12].

Recently, the results of three multicenter randomized controlled trials for Japanese and Taiwanese with metastatic and locally advanced PC have been reported (the Japan Clinical Cancer Research Organization PC-01 (JACCRO PC-01) phase II study, the GEMSAP phase II study, and the GEST phase III study) [13–15]. These studies have examined whether OS, progression-free survival (PFS), or objective response rate (ORR) using Gem with S-1 (GS) is superior to that using Gem alone.

In order to increase the statistical power of the analyses, we performed a pooled analysis of published or presented data from the three major studies and examined whether OS with GS is superior to that for Gem alone in patients with locally advanced PC.

Materials and methods

Study profiles

In the JACCRO PC-01 study, 117 patients were enrolled from 16 hospitals between March 2007 and August 2010. In the GEMSAP study, 106 patients were enrolled from six hospitals between July 2006 and February 2009. In the GEST study, 834 patients were enrolled from 75 hospitals between July 2007 and October 2009. A total of 193 patients with locally advanced PC (T4N0-1 and M0) were included in these trials, comprised of 31 patients from the JACCRO study, 28 patients from the GEMSAP study, and 134 patients in the GEST study. Table 1 shows the study profiles in detail. Other inclusion criteria were reported previously [13–15].

Locally advanced PC was defined as having surgically unresectable PC due to vascular involvement (portal vein or supra-mesenteric vein), including the celiac artery or supra-mesenteric artery, with no distant metastases on radiological examination using multidetector contrast-enhanced computed tomography, magnetic resonance imaging, or ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET).

The flow diagram for this study is shown in Figure 1. All patients gave written informed consent before enrollment. The three studies were conducted in accordance with the principles of the Declaration of Helsinki. Also, these three studies were registered with Clinical Trials.gov (NCT00514163 for the JACCRO PC-01 study, NCT00498225 for the GEST study) and in the UMIN Clinical Trials Registry (UMIN000000498 for the GEMSAP study) and were approved by the ethics committee or institutional review board of each participating center.

Treatments

In the three studies, enrolled patients were primarily assigned to receive either Gem or GS. Patients were centrally registered, and treatments were assigned by the modified minimization method. The Gem-group regimen consisted of intravenous 1000 mg/m^2 Gem on days 1, 8, and 15, repeated every 4 weeks. The GS-group regimens are shown in Table 1.

Overall survival was determined as the time from the date of randomization to the date of death due to any cause and was censored at the date of the last follow-up for surviving patients. PFS was counted from the date of random assignment to the date of death without progression or of progression as confirmed by the investigator's assessment. The ORRs were reported as best achieved response rates. Computed tomography or magnetic resonance imaging was performed every 4–8 weeks until disease progression, and response was assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 [16].

Statistical analysis

The primary endpoint was overall-survival, and secondary endpoint was progression free survival. All analysis was

Table 1 Profiles of the three trials

Enrollment period	GEMSAP		JACCRO PC-01		GEST	
	July 2006–February 2009		March 2007–August 2010		July 2007–October 2009	
	GEM (n = 13)	GS (n = 15)	GEM (n = 18)	GS (n = 13)	GEM (n = 66)	GS (n = 68)
Age (years)	69 (60–83)	67 (52–80)	63.5 (50–73)	62 (48–74)	67.5 (54–79)	64 (43–83)
Female/Male	7/6	4/11	9/9	5/8	28/38	32/36
PS (0/1–2)	9/4	10/5	12/6	13/0	48/18	54/14
H/BT (%)	46/54	67/33	33/67	15/85	55/45	58/42
Tumor size (mm)	NA	NA	42 (20–80)	41 (27–80)	37.5 (20–110)	40 (19–97)
CA19-9 (U/l)	812 (1–10,400)	421 (1–4,550)	834 (3–15,079)	524 (1–1,830)	278 (0.1–27,160)	172 (0–151,000)
Treatment schedule (GS)	GEM (1,000 mg/m^2, day 1, 15 q4w) TS-1 (80*, 100**, 120***mg/body d1-14)		GEM (1,000 mg/m^2, day 1, 8 q3w) TS-1 (80*, 100**, 120***mg/body d1-14)		GEM (1000 mg/m^2 day 1, 8 q3w) TS-1 (60*, 80**, 100***mg/body d1-14)	

BT pancreatic body and tail, *GS* Gem with S-1, *H* pancreatic head, *PS* performance status

* BSA <1.25 m^2, ** 1.25 ≤ BSA < 1.5, *** BSA ≥ 1.5

conducted on an intention-to-treat basis and all randomly assigned patients were included in the analyses according to the allocated treatment. Trial level hazard ratio (HR) and 95% confidence interval (CI) were obtained for each survival outcome. A general variance-based method was used to estimate the pooled HR and 95% CI [17]. Heterogeneity of the effect across trials was assessed by the χ^2 statistic with 2 degrees of freedom. A fixed effect approach was adopted unless there was evidence of significant heterogeneity. All statistical tests were two-sided, and P-values of 0.05 or less were considered to be statistically significant. All statistical analyses were conducted with Review Manager 5.2.

Results

Overall survival

The OS rate was reported in the three trials [13–15], which comprised 193 patients with locally advanced PC, of whom 97 received Gem alone and 96 received the GS combination. The treatment quality of each trial was evaluated (Table 1). The median OS for the GS treatment in the JACCRO PC-01, GEMSAP, and GEST studies was 14.8 (95% CI; 9.5–23.8), 23.9 (13.5–26.4), and 15.9 (13.0–20.1) months, and that for Gem was 8.8 (5.0–20.9), 11.0 (5.8–23.6), and 12.7 (9.7–14.9) months, respectively. Meta-analysis of the pooled data demonstrated that the overall risk of death was significantly different for the GS and GEM alone chemotherapies (HR = 0.673, 95% CI: 0.488–0.929, P = 0.016; Fig. 2).

Progression-free survival

The median PFS for GS in the JACCRO PC-01, GEMSAP, and GEST studies was 12.0 (3.8–15.2), 12.6 (3.4–16.5), and 10.7 (7.7–12.9) months, and that for Gem was 4.1 (2.0–6.6), 8.1 (2.2–13.0), and 6.2 (4.5–8.1) months, respectively. In our meta-analysis of the pooled data GS significantly improved PFS in patients with locally advanced PC compared with Gem (HR = 0.596, 95% CI: 0.437–0.811, P = 0.001; Fig. 3).

Objective response rate

The analysis of ORR was based on 165 events (85.5%) among the 193 patients. The ORR of patients with locally advanced PC in the GS group in the JACCRO PC-01, GEMSAP, and GEST studies was 23.1, 26.7, and 30.0%, and that for the Gem treatment it was 5.6, 7.7, and 9.0%, respectively. The random-effect pooled estimate for the 165 patients evaluated for ORR showed that in the GS treatment

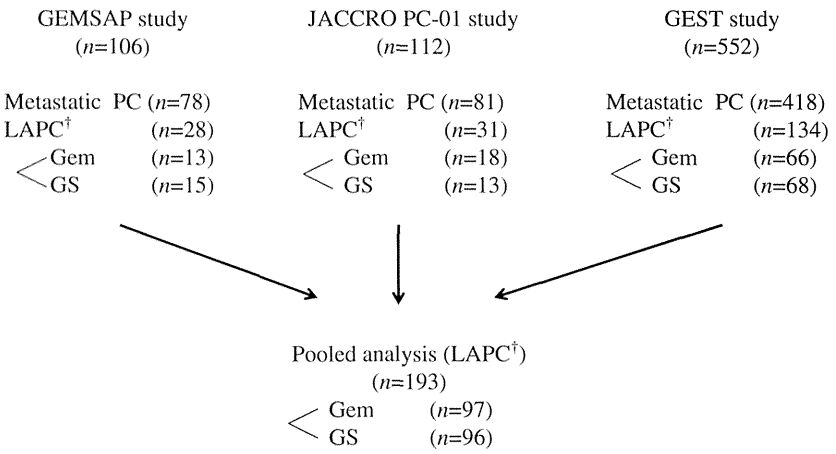

Fig. 1 Flow chart of patients. *LAPC*† locally advanced pancreatic cancer, *Gem*†† Gemcitabine, *GS*††† Gemcitabine with S-1

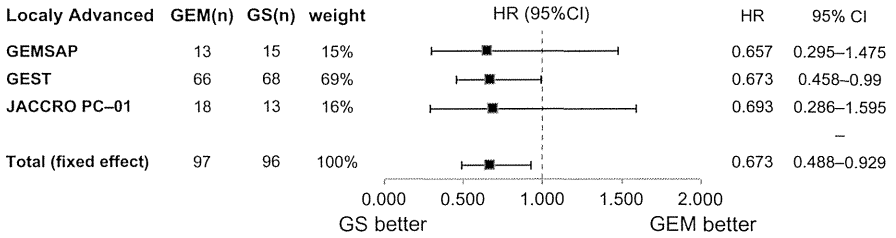

Fig. 2 Forest plots of hazard ratios (HRs) for overall survival (OS) from three randomized trials (GEST, GEMSAP, and JACCRO PC-01 studies) of GS compared with Gem, as first-line therapy in patients with locally advanced PC. *CI* confidence interval, *HR* hazard ratio, *n* number of patients

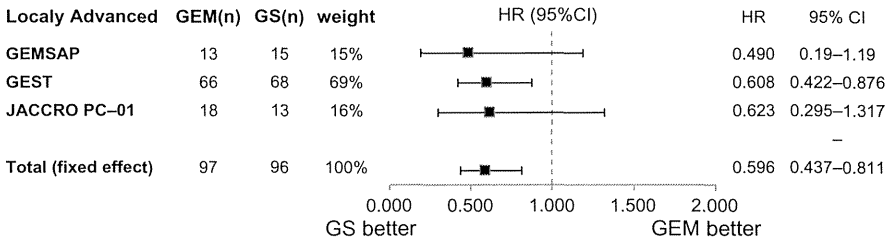

Fig. 3 Forest plots of hazard ratios (HRs) for progression-free survival (PFS) from the three randomized trials of GS compared with Gem, as first-line therapy in patients with locally advanced PC. *CI* confidence interval, *HR* hazard ratio, *n* number of patients

ORR was significantly increased (28.4% for the GS group versus 8.3% for the Gem group; $P = 0.001$).

Discussion

Gem is widely used as a standard systemic chemotherapeutic agent for advanced PC [2]. S-1 is a new oral fluoropyrimidine, and a phase II trial of S-1 involving patients with metastatic PC reported a good tumor response rate (38%) and improved survival (median, 9.2 months) [18]. Thus, S-1 was approved for the indication of PC in Japan in 2006. Furthermore, the GEST phase III trial, clearly showed that S-1 was not inferior to Gem in terms of OS rate in patients with metastatic and locally advanced PC in Japan and Taiwan [13]. Since there are only a few chemotherapeutic agents approved for the treatment of PC, the combination of Gem and S-1, that is, GS therapy, has been expected to exert a better effect. Although the GEST study showed that patients in the GS group had significantly higher incidences of grade 3 or worse leukopenia (38% vs. 19%), neutropenia (62% vs. 41%), thrombocytopenia (17% vs. 11%), rash (4.1% vs 0.7%), diarrhea (4.5% vs. 1.1%), vomiting (4.5% vs. 0,7%), and stomatitis (2.2% vs 0.0%) than patients in the GEM group, GS therapy is reportedly well tolerated [13–15].

Recently, the results of three multicenter randomized controlled trials for Asian patients with locally advanced and metastatic PC have been reported (JACCRO PC-01, GEMSAP, and GEST). Those trials addressed whether OS, PFS, or ORR could be improved when using GS compared to Gem alone. In the GEMSAP study, GS demonstrated a longer median PFS and higher 1-year survival rate than with Gem monotherapy. The GS regimen improved OS of 4.7 months. However, the difference between GS and Gem alone was not statistically significant. The JACCRO PC-01 study also showed significant superiority for GS in ORR,

PFS, and OS. However, the GEST study showed significantly longer PFS but failed to demonstrate superiority of OS. These discrepancies may be explained by differences in sample size as well as schedule or planned dose intensity of each agent in these three trials. Taken together, only the JACCRO PC-01 study showed a significant survival benefit in favor of GS, while no significant improvement in OS was confirmed in the GEST and GEMSAP studies.

Although there may be substantial differences in oncological behavior and patient prognosis between locally advanced and metastatic PC, those three clinical trials included both types of advanced PC. Three randomized trials included patients with metastatic pancreatic cancer as well as localized unresectable pancreatic cancer. Consensus report of the national cancer institute clinical trials planning meeting on pancreas cancer treatment suggested that localized unresectable PDAC must be studied in trials that do not include patients with metastatic disease because of the differences in natural history and the potential impact of radiation therapy on survival in patients with localized disease. We firmly believe that the current study provided useful information in localized unresectable pancreatic cancer for the future trial of this setting [19].

In the subgroup analyses of the GEST study, the GS group showed a favorable HR of 0.67 for OS in patients with locally advanced disease. Furthermore, the ORR of GS in the JACCRO PC-01 and GEST studies for locally advanced PC was significantly higher than for Gem. In addition, all three trials showed that GS treatment significantly improved PFS over Gem. These data suggest that the GS combination may be the most effective treatment for locally advanced PC. However, to our knowledge, there is no prospective study investigating GS in the treatment of patients with locally advanced PC without metastatic lesions. Therefore, we combined the data obtained from the three randomized controlled trials and performed a pooled analysis in which GS significantly improved OS, with an HR of 0.673 in patients with locally advanced PC compared with Gem.

Adjuvant surgery is a newly emerging concept in the treatment of PC. In patients with initially unresectable PC, chemotherapy or chemoradiotherapy has occasionally shown a significant antitumor effect, leading to substantial shrinkage of the primary tumor and followed by radical surgical resection. In fact, it has recently been reported that adjuvant surgery has shown unexpectedly favorable prognosis [20]. Furthermore, adjuvant surgery may have the potential to become curative treatment for the patient with initially unresectable advanced PC. Therefore, introduction of chemotherapy with better clinical response may be critical. At present, based on previous reports and this pooled analysis, GS may be the first choice for locally advanced PC. In the randomized phase III ACCORD-11 trial, the ORR in the FOLFIRINOX arm was as high as 32% compared with 9% in the Gem arm. In this pooled analysis, GS showed a similar high ORR (28.4%) to FOLFIRINOX. Therefore, for the prospective or randomized clinical trials to compare GS with FOLFIRINOX for locally advanced PC in terms of the rate of introduction of adjuvant surgery, safety and long-term prognosis should be considered.

In addition, the combination of external beam radiation therapy (EBRT) with 5-fluorouracil has been accepted as standard care for locally advanced PC [21–24]; however, it has not been shown to be superior to chemotherapy alone in the gemcitabine era [25]. Two randomized controlled trials comparing chemoradiation therapy with Gem alone have been conducted. A French group reported an inferior outcome with radiation therapy plus 5-FU and cisplatin compared to chemotherapy with Gem alone [26]. The ECOG study demonstrated that radiation therapy plus Gem had a superior survival outcome to Gem alone [27]. Thus, these two recent randomized controlled trials comparing chemoradiation therapy with Gem alone demonstrated conflicting survival results. It remains unclear whether chemoradiation therapy or chemotherapy alone has a better outcome in patients with locally advanced PC. This clinical question should also be evaluated in the future.

There were some limitations in this pooled analysis. First, this analysis included two phase 2 studies and only one phase 3 study. Second, each study used different regimen of GS (GEMSAP: GEM (day 1, 15 q4w)/TS-1 (d1-14), JACCRO PC-01: GEM (day 1, 8 q3w)/TS-1 (day 1-14), GEST: GEM (day 1, 8 q3w)/TS-1 (day 1-14) (Table 1)). Third, there was a relatively small number of patients despite the pooled analysis. Fourth, this analysis is based on published data instead of individual, updated data. These limitations of this analysis may result in some bias. However, such a pooled analysis excludes the ability to verify statistical analysis.

In conclusion, this pooled analysis has demonstrated that OS, PFS as well as ORR in patients receiving GS were superior to those treated with Gem. Therefore, GS could be one of the effective candidates for the standard first-line therapy for locally advanced PC.

Conflict of interest None declared.

Author contribution Study design: Hiroaki Yanagimoto. Acquisition of data: Hiroaki Yanagimoto, Hiroshi Ishii and Hiroyuki Isayama. Analysis and interpretation: Hiroaki Yanagimoto and A-Hon Kwon. Manuscript drafted by: Hiroaki Yanagimoto and Sohei Satoi. Revision: Hiroshi Ishii and Yousuke Nakai and Masato Ozaka and Takaaki Ikari and Kazuhiko Koike and Hideki Ueno and Tatsuya Ioka and Sohei Satoi and Masayuki Sho and Takuji Okusaka and Masao Tanaka and Toshio Shimokawa and A-Hon Kwon1and Hiroyuki Isayama. Statistical advice: Toshio Shimokawa.

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Neoadjuvant Gemcitabine-based Accelerated Hyperfractionation Chemoradiotherapy for Patients with Borderline Resectable Pancreatic Adenocarcinoma

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Objective: We report the response to pre-operative gemcitabine-based chemoradiotherapy for pancreatic adenocarcinoma.
Methods: Thirty-five consecutive patients with borderline resectable pancreatic adenocarcinoma of UICC Stage II or III with portal vein invasion or tumor abutment of artery received radiotherapy (twice daily fractions of 1.5 Gy, 5 days/week, total dose: 36 Gy; 30 Gy for Phase I Level 1) with weekly intravenous infusions of gemcitabine (400, 600 and 800 mg/m^2) at Days 1 and 8 for Phase I and 800 mg/m^2 for Phase II. Restaging was repeated after completion of chemoradiotherapy.
Results: Twenty-six of the 35 (74.3%) patients underwent resection. The dose-limiting toxicities were Grade 4 neutropenia and thrombocytopenia. The recommended regimen was total radiation dose of 36 Gy with gemcitabine 800 mg/m^2. Surgical resection was conducted in 11 of the 15 (73.3%) patients in Phase I study and 15 of the 20 (75.0%) in Phase II. After recommended dose chemoradiotherapy and surgical resection, the median disease-free survival was 17.4 months (5-year survival rate = 14.3%). The median overall survival time and 5-year survival rate were 41.2 months and 28.6%, respectively, for the 21 patients who underwent resection and 10.0 months and 0%, respectively, for those 5 who did not ($P = 0.004$).
Conclusion: Our pre-operative gemcitabine-based chemoradiotherapy was well tolerated and safe.

Key words: pancreatic cancer – gemcitabine – neoadjuvant

INTRODUCTION

Pancreatic cancer is one of the leading causes of tumor-related mortality. Although long-term survival is only possible with resection, the prognosis of patients after complete resection is often poor since most patients have occult distant metastasis at the time of resection. Consequently, surgical resection alone only provides minimal survival benefits. In this regard, treatment of pancreatic adenocarcinoma Union for International Cancer Control (UICC) Stage II or III is challenging, since resection is often associated with a microscopically positive margin of resection and likely results in local recurrence (1). Recently, significant improvements in disease-free and overall-survival have been observed in large trials of adjuvant chemotherapy (2,3). Especially, pre-operative chemoradiation seems to improve locoregional control. Thus, multimodal approaches using chemoradiation first followed by surgery and adjuvant chemotherapy seem to improve locoregional control, distant metastasis and survival. Pre-operative

chemoradiation may also avoid useless surgery in patients with occult distant metastasis or rapidly progressive disease (4).

Chemoradiation using 5-fluorouracil (5FU) has been the standard therapy for locally advanced pancreatic cancer, with a reported 1-year survival rate ranging from 17 to 28% (5–11). Recently, gemcitabine (difluorodeoxycytidine; GEM), a novel nucleoside analog, was reported to have a better effect than 5FU in advanced pancreatic cancer (12). However randomized controlled trial indicated the addition of GEM to adjuvant 5FU-based chemoradiation was associated with a survival benefit, although this improvement was not statistically significant (13). Another randomized controlled trial compared adjuvant GEM with 5FU plus folinic acid did not result in improved overall survival in patients with completely resected pancreatic cancer (14). Twice-a-day continuous radiotherapy with acceleration is a promising modality for irradiation of advanced pancreatic cancer. Accelerated hyperfractionation radiation reduces the total treatment time and repopulation of tumor cells between sessions, resulting in improved local control. In the present study, we applied pre-operative accelerated hyperfractionation radiation with GEM. Specifically, we conducted Phase I and II studies to define the maximum tolerated dose and recommended dose (RD) (Phase I) and assess the efficacy and tolerability of the combination therapy (Phase II).

PATIENTS AND METHODS

Eligibility and Evaluation

A total of 35 patients with not previously treated, borderline resectable pancreatic adenocarcinoma were admitted and treated at Osaka university hospital between January 2002 and December 2006 (Table 1). The institutional review board approved the study and each patient provided a signed informed consent. The eligibility criteria were histopathological or cytologic diagnosis of pancreatic adenocarcinoma, non-metastatic disease of UICC Stage II or III, T3 with

Table 1. Patients' characteristics

	Phase I		Phase II		Total	
	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)
Gender						
Male	10	66.7	13	65.0	23	65.7
Female	5	33.3	7	35.0	12	34.3
Age						
Median	68		72		71	
(range)	(43–77)		(44–79)		(43–79)	
41–50 years	1	7.0	2	10.0	3	8.6
51–60 years	5	33.3	3	15.0	8	22.9
61–70 years	2	13.3	2	10.0	4	11.4
71–79 years	7	46.7	13	65.0	20	57.1
UICC stage						
IIa (T3N0M0)	7	46.7	10	50.0	17	48.6
IIb (T3N1M0)	2	13.3	1	5.0	3	8.6
III (T4N0M0)	4	26.7	9	15.0	13	37.1
III (T4N1M0)	2	13.3	0	0.0	2	5.7
Portion						
Head	11	73.3	15	75.0	26	74.3
Body–tail	4	26.7	5	25.0	9	25.7
Vascular involvement						
PV and/or SMV	9	60.0	11	55.0	20	57.1
CeA or SMA	2	13.3	2	10.0	4	11.4
PV/SMA and CeA/SMA	4	26.7	7	35.0	11	31.4
CA19-9						
Median	1566		272		541	
(range)	(164–14070)		(36–3468)		(36–14070)	