Clinical significance of neoadjuvant chemotherapy with gemcitabine plus S-1 for resectable pancreatic ductal adenocarcinoma

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Abbreviations: AC, adjuvant chemotherapy; AJCC, American Joint Committee on Cancer; BR, borderline resectable; CA, celiac artery; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CHA, common hepatic artery; CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; Dupan-2, pancreatic cancer associated antigen; FOLFIRINOX, fluorouracil/leucovorin plus irinotecan plus oxaliplatin; GN, gemcitabine plus nab-paclitaxel; GS, gemcitabine plus S-1; HR, hazard ratio; LN, lymph node; MDCT, multidetector-row computed tomography; NAC, neoadjuvant chemotherapy; NCCN,

National Comprehensive Cancer Network; OS, overall survival; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; PR, partial response; PV, portal vein; R-PDAC, resectable pancreatic ductal adenocarcinoma; R, resectable; RDI, relative dose intensity; RFS, relapse-free survival; SD, stable disease; SMA, superior mesenteric artery; SMV, superior mesenteric vein; Span-1, S-pancreas-1; UFS, upfront surgery; UR, unresectable.

Keywords pancreatic cancer, neoadjuvant chemotherapy, adjuvant chemotherapy, gemcitabine, S-1

Abstract

Background Little is known about the efficacy of neoadjuvant chemotherapy (NAC) with gemcitabine plus S-1 (GS) on outcomes in patients with resectable pancreatic ductal adenocarcinoma (R-PDAC). This study aimed to investigate the clinical significance of NAC-GS on long-term outcomes.

Methods A total of 77 patients with R-PDAC who were scheduled for pancreatectomy between January 2012 and December 2017 were enrolled. Of these, 39 patients received NAC-GS (GS group) and 38 patients had upfront surgery (UFS group). Clinicopathological characteristics and postoperative outcomes were compared between the two groups.

Results Of 77 patients, each 1 patient did not undergo pancreatectomy due to the intraoperative non-curative factor in both groups. The median tumor size and the number of metastatic lymph nodes were significantly lower in the GS group than in the UFS group ($P = 0.002$ and $P = 0.017$). However, the 5-year overall survival and relapse-free survival rates were comparable between the GS and UFS groups (26.1% and 8% vs. 21.5% and 12.8%, $P = 0.930$ and $P = 0.764$, respectively). The R0 resection rate did not differ significantly between the two groups ($P = 0.122$).

Conclusion NAC-GS may not be recommended for patients with R-PDAC because the

survival benefit has not been demonstrated until now.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most fatal abdominal neoplasm with the 5-year overall survival (OS) rate of only 9% [1]. Although only surgical resection is the mainstay of curative treatment for patients with PDAC, the 5-year survival rate is an extremely poor, ranging from 6% to 30% [2-4], due to the high rate of cancer recurrence. In addition, surgical resection can be introduced for only 15-20% of patients with PDAC at the initial diagnosis [5, 6], because of the presence of distant metastasis or tumor invasion to the peripheral vessels including the common hepatic artery (CHA), superior mesenteric artery (SMA), and portal vein (PV). Therefore, improvement of the resectability is mandatory to give the chance of cure to the patients with PDAC.

The resectability classification of PDAC was introduced by the National Comprehensive Cancer Network (NCCN) guidelines and have been widely utilized recently in the world [7]. PDAC was classified into 3 categories: resectable (R), borderline resectable (BR), or unresectable (UR) based on the possibility of residual tumor status evaluated by contrast-enhanced multi-detectorrow computed tomography (MDCT). Although a better R0 resection rate can be achieved in patients with R-PDAC than in patients with BR- or UR-PDAC, the 5-year OS has been still unsatisfied [8-10].

Gemcitabine and S-1 are known to be key drugs of the improvement of survival in patients with PDAC [11, 12]. The combination therapy of gemcitabine plus S-1 (GS) has been chosen as standard therapy for patients with advanced PDAC in Japan until fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX) or gemcitabine plus nab-paclitaxel (GN) therapy are clinically introduced [13,14,15]. A randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer (GEST study) was conducted in Japan and Taiwan [13, 16]. Although the superiority of GS to gemcitabine was not proved in OS, the objective response rate and the median tumor shrinkage ratio were higher in the GS group than in the gemcitabine and S-1 groups (29.3% vs. 13.3% and 21.0%, respectively, and 20.9% vs. 7.0% and 7.9%, respectively). The combination of GS had an advantageous effect on tumor shrinkage, which may possibly make BR and UR resectable. These results indicate that GS may be a favorable regimen of neoadjuvant chemotherapy (NAC). The clinical trial of NAC-GS for patients with R- and UR- PDAC were conducted [17, 18]. These results have suggested that NAC-GS with good tolerability and safety may improve survival and R0 resection rate. However, the clinical significance of NAC-GS for patients with R-PDAC remains still unclear, because only a few papers are available for evaluating the clinical significance. Therefore, the aim of this study was to

investigate the difference in long-term outcome of patients with R-PDAC who underwent pancreatectomy between with- and without-NAC-GS and to clarify the clinical significance of NAC-GS.

Methods

A total of 131 patients with a clinical diagnosis of PDAC who were scheduled for elective surgery at the Department of Gastroenterological Surgery, Dokkyo Medical University Hospital, between January 2012 and December 2017 were retrospectively reviewed. Among these patients, those with R-PDAC without distant metastasis were selected for inclusion in this study. A diagnosis of R-PDAC was based on the findings of contrast-enhanced MDCT according to the NCCN guidelines version 2. 2018 [7]. R-PDAC was defined as meeting both no tumor contact with the celiac artery [CA], SMA, or CHA and no tumor contact with the superior mesenteric vein (SMV) or PV or $\leq$180 contact without vein contour irregularity. A distant metastasis was evaluated by the MDCT and/or magnetic resonance imaging, and/or positron emission tomography. Among the patients with R-PDAC, those who underwent NAC followed by surgery were categorized as the GS group, and those who had undergone surgery without NAC as initial

treatment were categorized as the upfront surgery (UFS) group. This study was approved by the ethics committee of Dokkyo Medical University (Ethical committee review-number R-15-8J).

Pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy with regional lymph node dissection was performed according to the tumor location. PV or SMV resection to achieve curative resection was undertaken if tumor invasion was recognized or suspected during the surgery. When distant metastases such as liver, extra-regional lymph nodes (LN), or peritoneal dissemination or tumor invasion to the CHA or CA were found during the surgery, the case was judged as inoperable. Postoperative complications were classified according to the Clavien-Dindo classification [19].

Pathological features of the resected specimens were classified according to the seventh edition of the Japanese Rules for Pancreatic Cancer and the eighth edition of the American Joint Committee on Cancer (AJCC) staging manual for pancreatic cancer [20, 21].

LN ratio was determined by dividing the number of metastatic LNs by the number of dissected LNs.

GS group

The dosage of gemcitabine and S-1 given to the patients who received NAC was based on the results of a phase II study of GS therapy [17, 22]. Gemcitabine was given at a dose of 1000 mg/m^2 on days 1 and 8 of each course. S-1 was provided orally at a dose of 40, 50, or 60 mg/m^2 twice daily according to body surface area (less than 1.25 m^2, 1.25–1.5 m^2, or over 1.5 m^2) for the first 14 consecutive days followed by a 7-day rest. Each course was repeated every 21 days. Patients received two courses of GS therapy. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used for evaluation of treatment related toxicities. Relative dose intensity (RDI) for gemcitabine and S-1 was calculated as the dose intensity achieved related to the standard schedule of each drug. Average RDI was calculated as the average of each RDI of gemcitabine and S-1. Response Evaluation Criteria in Solid Tumors (RECIST) were utilized to evaluate response rate [23]. Pathological response by the chemotherapy was categorized according to Evans' classification [24].

Statistical analysis

SPSS version 25.0 (IBM Japan, Tokyo, Japan) was used for all statistical analyses. Continuous data were expressed as medians with ranges and were compared using the

Mann-Whitney *U* test, while categorical data were compared using the chi-squared test or Fisher's test. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Uni- and multivariate analyses were performed using the log-rank test and Cox proportional hazards forward stepwise model was used to identify risk factors for OS. Differences at $P < 0.05$ were considered statistically significant.

Results

Preoperative patient characteristics

Seventy-nine patients (60.3%) with R-PDAC were treated during the same period. Flow chart of treatment course of patients with R-PDAC is shown in Figure 1. Thirty-eight patients underwent surgery without NAC (UFS group) and 39 patients initially received the GS regimen (GS group). The remaining 2 patients who received other regimen including GS 1 course followed by GN 1 course were excluded from the study. In the UFS group, 37 (97.4%) patients underwent pancreatectomy and 1 patient did not undergo pancreatectomy due to the liver metastasis. In the GS group, 38 patients (97.4%)

underwent pancreatectomy and 1 patient did not undergo pancreatectomy due to the para-aorta LN metastasis.

Table 1 shows the preoperative clinical data of the UFS and GS groups. There were no significant differences in terms of age, gender, tumor location, tumor size, biliary drainage, cerum tumor marker level such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), pancreatic cancer associated antigen (Dupan-2), S-pancreas-1 (Span-1), and Elastase-1 between the two groups.

Surgical outcomes

Surgical outcomes of the UFS and GS groups who underwent pancreatectomy listed in Table 2. There were no significant differences in type of surgery, PV resection, operation time, blood loss, postoperative complications, in-hospital death, postoperative hospital stay, and adjuvant chemotherapy (AC). AC such as gemcitabine (n = 12), S-1 (n = 52), and other (n = 2) had been used in 9, 20, and 2 UFS group patients and in 3, 32, and 0 GS group patients, respectively.

Tumor response to NAC

Table 3 exhibits the changes of clinical outcomes between pre- and post-GS therapy. The reduction rates of tumor markers including CEA, CA19-9, Dupan-2, Span-1, and Elastase-1 were -15.4% (-145.5–71.1), 39.9% (-108.2–94), 36.2% (-41.7–84.9), 40.7% (-100–82.5), and 29.2% (-220–98.6), respectively. Four tumor markers except CEA decreased from the baseline after GS therapy. The reduction rate of tumor size was 19% (-16–46.5). None of the patients showed a complete response (CR) and progressive disease (PD), 6 patients showed a partial response (PR), and 33 patients showed a stable disease (SD). Median relative dose intensity (RDI) of gemcitabine and S-1 was 100% (40–100) and 100% (28.6–100), respectively. The average RDI was 90.8% (39.3–100). Patients lost 1.9 kg body weight (-3–15.1) during the GS therapy.

When a correlation of maximum tumor size measured by preoperative CT and the resected specimen was compared, there was a good correlation (Spearman correlation coefficients; $R^2 = 0.616$, $P = 0.01$, data not shown).

Toxicity and adverse events

The GS-related toxicities are noted in Table 4. All patients were assessable for adverse events. Of 39 patients, 14 (35.9%) completed two planned courses without any dose

reduction and 11 (28.2%) completed the courses with dose reduction, but 14 (35.9%) could not complete two courses of GS therapy. The hematological toxicities such as neutropenia, thrombocytopenia, and anemia commonly occurred in 66.7%, 53.8%, and 53.8%, respectively. The common non-hematological toxicities were rash and elevations in aspartate aminotransferase and alanine aminotransferase (41%, 38.5%, and 38.5%, respectively). The most common grade 3/4 adverse events were neutropenia (46.2%).

Pathological outcomes

Pathological outcomes of the SF and GS groups are summarized in Table 5. The maximum tumor size was significantly smaller in the GS group than in the SF group (P = 0.002). The number of dissected LNs were similar between the two groups. However, the number of metastatic LNs and LN ratio were significantly lower in the GS group than in the SF group (P = 0.017 and P = 0.014). Lymphatic invasion was less observed in the GS group than in the SF group (P = 0.050). However, level of differentiation, venous invasion, neural invasion, PV invasion, and residual tumor status were similar between the two groups. Histological response evaluation according to Evans' classification disclosed that grade I, IIa, IIb, and III were 9 (23.7%), 24 (63.2%), 4 (10.5%), and 1

(2.6%) of 38 patients, respectively.

Overall survival and relapse-free survival

The median follow-up period was 24.2 months (0.6–84.2) for 75 patients who underwent pancreatectomy. The 5-year OS and relapse-free survival (RFS) rates in the SF and GS groups were 21.5% and 12.8%, and 26.1% and 8%, respectively ($P = 0.930$ and $P = 0.764$, respectively) (Fig 2A, B). The median OS and RFS period in the SF and GS groups were 24.3 months and 15.6 months, and 21.5 months and 12.7 months, respectively. Recurrence was observed in 30 patients (81.1%) in the SF group and 27 patients (71.1%) in the GS group ($P = 0.309$).

Risk factors for survival

Table 6 shows the results of uni- and multivariate analyses of risk factors for OS. Five of 17 factors were found to be significant by univariate analysis: age ≥75 years, blood transfusion (+), T3, 4, LN ratio >0.1, and AC (-). Multivariate analysis revealed that T3, 4 (hazard ratio [HR], 2.900; 95% confidence interval [CI], 1.308 – 6.428; $P = 0.009$), LN ratio >0.1 (HR, 2.040; 95% CI, 1.147 – 3.628; $P = 0.015$), and no AC (HR, 3.569; 95%

CI, 1.636 – 7.783; $P = 0.001$) were independent risk factors for poor OS.

Discussion

NAC offers several advantages over upfront surgery, including early delivery of anti-cancer drugs to control minute metastasis, high tolerability of multi-agent regimens, and a higher R0 resection rate, that may lead to a better prognosis. The various regimens including GS, GN, or FOLFIRINOX as NAC have been studied and reported to improve postoperative survival [17, 18, 26-28]. However, most studies were intended for patients with BR- or UR-PDAC who have a possible increase of R1 resection rate. It is ambiguous whether the use of NAC is really beneficial for patients with R-PDAC. Therefore, we retrospectively investigated the clinical significance of NAC-GS for only patients with R-PDAC classified by the NCCN guidelines who were scheduled for surgery.

NAC has two potential risks. First, toxicities of NAC may affect the perioperative morbidity and mortality. In this study, the most common hematological and nonhematological toxicities were neutropenia (66.7%) and rash (41%) with grade 3/4 of 46.2% and 10.3%, respectively (Table 4). There was no NAC-GS-related mortality. All patients who had adverse events recovered and were scheduled for surgery. Comparable

results have been reported previously in a phase II trial [17]. No increase in operation time, blood loss, morbidity, and mortality were observed (Table 2). Therefore, the use of NAC-GS will be feasible and safe for patients with R-PDAC. Second, disease may progress and become unresectable during the course of NAC. Motoi et al reported that 6 (3.2%) of 185 patients with R-PDAC who received NAC with various regimens (mainly gemcitabine monotherapy) were not operated due to the tumor progression [29]. However, all patients who received NAC-GS did not become unresectable and had a planned surgery in this study. Accordingly, NAC-GS may be useful in control of tumor progression in short course treatment.

NAC-GS decreased the levels of tumor markers such as CA19-9, Dupan-2, Span-1, and Elastase-1 except CEA before and after the treatment (Table 3). Because 28 (71.8%) of 39 patients showed the normal level of CEA before NAC-GS, only a little change of CEA from the baseline level was observed after NAC-GS. Therefore, NAC-GS might not decrease the median levels of CEA. Thirty-seven (94.9%) of 39 patients had tumor shrinkage with the median reduction rate of 19% by NAC-GS. Although the number of dissected LNs were equivalent between the SF and GS groups, the number of metastatic LNs and LN ratio were significantly lower in the GS group than in the SF group (P = 0.017 and P = 0.014). Nagakawa et al also demonstrated that neoadjuvant therapy was

beneficial to decrease the number of metastatic LNs in propensity score-matched 594 patients with borderline resectable pancreatic cancer [33]. Thus, NAC could be expected to decrease the LN metastasis as previous studies also reported the similar results [27, 29]. The proportion of pathological Stage I was significantly higher in the GS group than in the SF group (Table 5). These results indicate that the use of NAC-GS contributes to down-staging of the tumor in patients with R-PDAC.

In terms of the long-term outcome, the 5-year OS and RFS rates did not differ significantly between the UFS and GS groups ($P = 0.930$ and $P = 0.764$) (Figure 2). It is suggested that CA19-9 response to NAC is associated with postoperative survival [30]. However, tumor markers including CEA, CA19-9, Dupan-2, Span-1, and Elastase-1 response to NAC had no impact on postoperative survival in this study ($P = 0.209$, $P = 0.079$, $P = 0.877$, $P = 0.060$, and $P = 0.289$, respectively). Xia et al reported that there was no correlation between degree of radiologic response according to RECIST and degree of pathological response according to Evans' classification in patients with BR-PDAC [31]. Furthermore, regarding pathological response, patients with Evans' grade IIb-IV exhibited improved OS compared to patients with Evans' grade I-IIa (median OS, 22.7 vs. 10.5 months, $P = 0.0383$). In the present study, a survival advantage for patients with Evans' grade IIa-III compared to patients with Evans' grade I was found (median

OS, 26.8 vs. 11.7 months, $P = 0.001$). However, it may be difficult to predict patients who will potentially benefit pathological response before the initiation of NAC-GS.

With regard to why NAC-GS had no impact on postoperative survival in patients with R-PDAC despite the fact that NAC-GS contributed to down-staging of the tumor, two possibilities can be suggested. First, there may be some difference in the residual tumor status between the UFS and GS groups. Masui et al reported that the frequency of R0 resection was significantly higher in the NAC-GS (+) group than in the NAC-GS (-) group in patients with BR-PDAC (87% vs. 53%, $P = 0.002$) [18]. It is reported that the R0 resection rate of upfront surgery for BR-PDAC patients ranges from 53% to 77% [18, 26, 29, 33]. The R0 resection rate deteriorates in patients with BR-PDAC than in patients with R-PDAC due to the possible invasion of peripheral vessels and tissues. Conversely, it is more likely to improve the R0 resection rate by down-staging effects of NAC that may lead to prolonged survival. However, in patients with R-PDAC, surgical resection without NAC itself can achieve a higher R0 resection rate, ranging from 81.3% to 90.2% [9, 29, 32]. Therefore, it may be difficult to seek the further improvement of R0 resection rate by NAC. Zhan et al demonstrated that NAC has not been proven to be beneficial and should be considered with caution in patients with R-PDAC in a systematic review and meta-analysis of prospective studies [32]. Second, there may be a strong impact of AC on

postoperative survival. Surgical resection followed by AC including gemcitabine or S-1 is the only treatment strategy currently available with the chance of cure [11, 12, 23]. Multivariate analysis revealed that the use of AC was the most powerful prognostic factor in this study cohort (Table 6). Sixty-six (88%) of 75 patients received AC, of whom 12 (18.2%), 52 (78.8%), and 2 (3%) had gemcitabine, S-1, and other, respectively. There were no significant differences between the UFS and GS groups regarding the number of patients who received AC and the periods until initiation of AC after surgery (56 days vs. 65 days, $P = 0.111$). The use of NAC-GS did not affect the initiation of AC. S-1 is often chosen as AC in Japan since Uesaka et al have been demonstrated the superiority of S-1 to gemcitabine for resected PDAC in a phase III trial [12]. The effectiveness of AC for postoperative survival may be superior to that of NAC in patients with R-PDAC. Because surgical invasiveness such as operation time, blood loss, and concomitant vascular resection will be light in patients with R-PDAC than in patients with BR- or UR-PDAC [29, 30], it may be likely to initiate AC without dose reduction.

LN ratio >0.1 was associated with the poor survival in multivariate analysis. Pawlik et al demonstrated that a high LN ratio portends poor tumor biology and, as expected, a worse overall survival [34]. Although NAC-GS was useful to decrease the LN ratio, patients who remains a high LN ratio might have a poor biological malignant potential.

Our study had several limitations that need to be pointed out. This was a single-center retrospective study that analyzed data for only a small number of patients with R-PDAC in a 6-year period. Therefore, further prospective studies with large numbers of patients will be required in order to reach definitive conclusions. At present, a randomized phase II/III trial of NAC with GS versus upfront surgery for resectable pancreatic cancer has begun, we have to wait for the results of the study [35].

In conclusion, although the use of NAC-GS contributes to down-staging of the tumor, NAC-GS may not be recommended for the treatment of patients with R-PDAC because the survival benefit has not been demonstrated.

Conflict of interest The authors have no conflicts of interest to declare.

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Figure legends

Fig 1. Flow chart of treatment course of patients with R-PDAC from 2012 to 2017.

Fig 2. **(A)** Overall survival (OS) and **(B)** relapse-free survival (RFS) in the SF (n = 37) and GS (n = 38) groups. There were no significant differences in the OS and RFS between the two groups.