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Clinical utility of the S-1 dosage formula in neoadjuvant chemotherapy with gemcitabine plus S-1 for resectable pancreatic cancer

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Abstract

Background

Neoadjuvant gemcitabine plus S-1 is standard for resectable pancreatic cancer in Japan, but the utility of the Booka–Boku–Takeuchi (BBT) formula for S-1 dosing is unclear.

Methods

In this retrospective study of patients with resectable pancreatic cancer who underwent neoadjuvant gemcitabine plus S-1 followed by surgery, patients were classified by the ratio of the actual starting S-1 dose to the BBT-calculated dose into low-dose (< 0.9), equal-dose (0.9 to < 1.1), and high-dose (≥ 1.1) groups.

Results

Among 97 patients (low-dose, *n* = 12; equal-dose, *n* = 37; high-dose, *n* = 48), median tumor shrinkage rates were 5.9%, 12.2%, and 13.1% (*P* = 0.02), and median recurrence-free survival was 9.0 months, not reached, and 19.7 months. Compared with the equal-dose group, hazard ratios (HR) for recurrence-free survival were 3.15 (95% confidence interval [CI] 1.28–7.77, *P* = 0.01) in the low-dose group and 2.10 (95% CI 1.06–4.13, *P* = 0.03) in the high-dose group; for overall survival, HR was 2.97 (95% CI 1.04–8.49, *P* = 0.04) and 1.69 (95% CI 0.75–3.79, *P* = 0.21), respectively. Grade ≥ 3 mucositis occurred in 0%, 0%, and 19% (*P* < 0.01), and S-1 dose reduction or discontinuation in 33%, 43%, and 69% (*P* = 0.02). Equal-dose status (*P* = 0.02) and a normal carbohydrate antigen 19 − 9 level (*P* = 0.03) were independent favorable factors for recurrence-free survival.

Conclusions

S-1 dose adjustment using the BBT formula may improve outcomes in patients receiving neoadjuvant gemcitabine plus S-1 for resectable pancreatic cancer.

Introduction

Pancreatic ductal adenocarcinoma remains one of the most lethal malignancies, with a 5-year overall survival rate of approximately 10% or higher [1]. Surgical resection followed by adjuvant chemotherapy has been the standard treatment for resectable pancreatic cancer (RPC). However, the high postoperative recurrence rate has shifted the therapeutic paradigm toward neoadjuvant chemotherapy (NAC) [2, 3]. The primary objectives of NAC are to eliminate micrometastatic disease, improve the R0 resection rate, and select patients most likely to benefit from invasive surgery. In Japan, the phase III Prep-02/JSAP-05 trial established NAC with gemcitabine and S-1 (NAC-GS) as the standard of care for

RPC, demonstrating a significant survival benefit over upfront surgery followed by adjuvant chemotherapy [2].

S-1 is an oral agent containing tegafur, a prodrug of 5-fluorouracil (5-FU), and gimeracil, an inhibitor of dihydropyrimidine dehydrogenase (DPD), a key enzyme in 5-FU metabolism, which maintains high 5-FU concentrations. In Asia, the standard dose of S-1 is determined by body surface area (BSA) as 80 mg/m²/day [4]. Because gimeracil is predominantly excreted renally, renal impairment increases gimeracil exposure, leading to excessive DPD inhibition and high blood 5-FU concentrations [5, 6]. A postmarketing survey of S-1 revealed a high incidence of adverse events in patients with impaired renal function [7].

Owing to the lack of a standardized pharmacokinetic dosing model (such as the Calvert formula for carboplatin), S-1 dose reduction is empirically recommended for patients with creatinine clearance (CLcr) < 80 mL/min. Two prospective pharmacokinetic studies in patients with cancer and various renal functions proposed an S-1 dosage formula (the Booka–Boku–Takeuchi [BBT] formula) based on BSA, sex, and renal function to achieve the target area under the concentration–time curve (AUC) of 5-FU [6, 8, 9]: recommended daily S-1 dose = target AUC × (14.5 + 8.23 × sex [0 for female and 1 for male] + 0.301 × CLcr) × BSA. Nomograms have also been proposed to determine actual S-1 doses adjusted for commercially available tablet strengths (20 and 25 mg) to obtain the target AUC (1447.8 ng·h/mL) for individual sex, BSA, and CLcr.

Although the clinical relevance of the BBT formula has been reported in patients with gastric cancer receiving S-1-based chemotherapy [10], its utility in patients with RPC receiving NAC-GS has not been fully elucidated. In particular, data on the relationship between BBT-based dose adjustment and long-term oncological outcomes, such as recurrence-free survival (RFS) and overall survival (OS), are limited.

We therefore retrospectively evaluated the relationship between S-1 exposure, classified by the ratio of the actual administered dose to the BBT-calculated dose, and the efficacy and safety of NAC-GS in patients with RPC, to determine whether adherence to BBT-based dosing can improve clinical outcomes.

Materials and methods

Study population

This study included patients with RPC who received NAC-GS followed by surgery between 2019 and 2024 at our institution. RPC was defined as a histologically confirmed pancreatic tumor with R0 resectability, no involvement of the hepatic, celiac, or superior mesenteric arteries, and no detectable distant metastasis [2]. Patients with resectable disease on imaging but suspected to be biologically borderline resectable because of elevated carbohydrate antigen 19 − 9 (CA19-9) levels (≥ 500 U/mL), and those unsuitable for surgery because of poor general condition or significant comorbidities, were excluded. This study was approved by the institutional review board of The University of Tokyo Hospital

(Approval No. 2058). The requirement for informed consent was waived because of the retrospective observational design, and an opt-out approach was adopted.

Treatment schedule

Patients with RPC received two cycles of NAC-GS followed by surgical resection. NAC-GS consisted of intravenous gemcitabine at 1000 mg/m² on days 1 and 8 and oral S-1 (40 mg twice daily for BSA < 1.25 m², 50 mg twice daily for BSA 1.25–1.50 m², and 60 mg twice daily for BSA > 1.50 m², on days 1 to 14) in a 21-day cycle [2]. In cases of disease progression or intolerable adverse events during NAC-GS, chemotherapy was discontinued immediately at the physician's discretion and surgery was performed, if possible. Because of the retrospective design, no predefined protocol for dose modification or prophylactic treatment of anticipated adverse events was applied. Dose modification was generally performed at the treating physician's discretion, particularly in patients who developed grade ≥ 3 hematological or grade ≥ 2 non-hematological adverse events.

S-1 dose classification

Patients were classified into three groups based on the ratio of the starting actual dose (AD) of S-1 to the BBT-calculated dose (BD): low dose (LD: AD/BD < 0.9), equal dose (ED: 0.9 ≤ AD/BD < 1.1), and high dose (HD: AD/BD ≥ 1.1). The AUC for each group was calculated from the linear relationship between AUC and S-1 dose: AUC = target AUC (1.4478 μg·h/mL) × AD/BD. Efficacy (response rate [RR], tumor shrinkage rate compared with baseline, RFS, and OS) and the incidence of adverse events (AEs) were retrospectively compared among the three groups.

Data collection

Clinical data, including age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), BSA, CLcr, primary tumor site (head, body, or tail), tumor markers (carcinoembryonic antigen [CEA] and CA19-9), tissue v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) status, and histological type, were collected retrospectively from the medical records. Relative dose intensity (RDI) was calculated as the total administered S-1 dose divided by the planned dose during the treatment period, and BBT-based RDI was calculated by dividing the total administered S-1 dose by the BBT-recommended dose for each patient. Using the primary tumor as the target lesion and following the Response Evaluation Criteria in Solid Tumors guidelines (v1.1), responses to NAC-GS were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) [11]. RR was defined as the proportion of patients achieving CR or PR, and the disease control rate (DCR) as the proportion achieving CR, PR, or SD. RFS was defined as the time from surgery to the first objective evidence of recurrence or death from any cause. OS was defined as the time from surgery to death from any cause or the date of last follow-up. AE severity was graded according to the Common Terminology Criteria for Adverse Events (v6.0) [12]. Histological therapeutic effects of NAC on the primary tumor were

evaluated on a 5-grade scale (grades 0–4) according to the Japanese Classification of Pancreatic Carcinoma (8th edition): grade 0 (no effect); grade 1a (mild effect), viable tumor cells accounting for more than 2/3 of the tumorous area; grade 1b (moderate effect), more than 1/3 but not more than 2/3; grade 2 (marked effect), 1/3 or less; grade 3 (extreme effect), less than 10%; and grade 4 (complete response), no viable tumor cells [13].

Statistical analysis

Data are presented as median (range) or count (proportion), as appropriate. Categorical variables were compared using Fisher's exact test, and continuous variables using the Kruskal–Wallis test; pairwise comparisons used Fisher's exact test or the Wilcoxon rank-sum test. Time-to-event analyses were performed using the Kaplan–Meier method, and groups were compared using the log-rank test. Median follow-up was estimated using the reverse Kaplan–Meier method. Multivariate Cox proportional hazards regression analysis was performed to adjust for possible confounders, including sex, age, ECOG PS, pathological type, primary tumor site, tissue *KRAS* status, CEA or CA19-9 elevation, AD/BD ratio, and adjuvant chemotherapy. Factors with $P < 0.05$ in the univariate analysis were included in the multivariate model (backward stepwise method based on the Bayesian information criterion). Multivariate analysis was not performed for an endpoint in which no factor met this criterion. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. Analyses were conducted using EZR version 1.61 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) and a modified version of R commander designed to add statistical functions frequently used in biostatistics [14].

Results

Cohort characteristics

Of 100 patients with RPC who underwent NAC-GS between July 2019 and December 2024, 3 were excluded: 1 had disease progression during NAC-GS, 1 developed cerebral infarction during NAC-GS and did not undergo surgery, and 1 received NAC-GS despite having biologically borderline resectable pancreatic cancer. Consequently, 97 patients who met the selection criteria were analyzed; 67 (69%) were male, and the median age was 73 years (range 47–89). Pretreatment ECOG PS was 0 in 77 patients (79%) and 1–2 in 20 (21%). Fifty-one patients (53%) had primary tumors in the pancreatic head. The median tumor size was 22.0 mm (range 10.1–46.1), median CEA was 3.4 ng/mL (0.9–36.7), and median CA19-9 was 81.0 U/mL (1.0–489). *KRAS* mutations were present in 78 patients (80%). Patients were classified as LD (n = 12), ED (n = 37), or HD (n = 48) (Table 1). The LD group consisted entirely of male patients who were significantly younger ($P < 0.01$) and had a larger BSA ($P < 0.01$), better CLcr ($P < 0.01$), and larger tumor diameters ($P = 0.01$). Females predominated in the HD group ($P < 0.01$), and *KRAS* wild-type cases were found exclusively in the ED group ($P = 0.02$). The AUC calculated from the actual S-1 dose differed significantly among the three groups ($P < 0.01$) (Online Resource 1). Postoperative

adjuvant chemotherapy with S-1 or gemcitabine monotherapy was administered to 100% of patients in the LD group, 81% in the ED group, and 83% in the HD group, with no significant difference (P = 0.33).

Table 1
Patient characteristics

Characteristic	Total (*n* = 97)	LD (*n* = 12)	ED (*n* = 37)	HD (*n* = 48)	*P* value
Age (years), median [range]	73 [47–89]	60 [47–84]	72 [54–89]	76 [49–85]	< 0.01
Sex					
Male	67 (69)	12 (100)	32 (86)	23 (48)	< 0.01
Female	30 (31)	0 (0)	5 (14)	25 (52)	
ECOG PS					
0	77 (79)	12 (100)	30 (81)	35 (73)	0.09
1–2	20 (21)	0 (0)	7 (19)	13 (27)	
Primary tumor site					
Head	51 (53)	7 (58)	19 (51)	25 (52)	0.92
Body and tail	46 (47)	5 (42)	18 (49)	23 (48)	
Tumor size (mm), median [range]	22.0 [10.1–46.1]	26.9 [13.6–46.1]	22.0 [10.4–37.6]	20.0 [10.1–32.4]	0.01
KRAS status					
Wild type	5 (5)	0 (0)	5 (13)	0 (0)	0.02
Mutant	78 (80)	11 (92)	28 (76)	39 (81)	
Unknown	14 (15)	1 (8)	4 (11)	9 (19)	
Histological type					
Adenocarcinoma	88 (91)	12 (100)	32 (86)	44 (92)	0.43
Anaplastic carcinoma	1 (1)	0 (0)	0 (0)	1 (2)	
IPMN-derived carcinoma	8 (8)	0 (0)	5 (14)	3 (6)	
Adjuvant chemotherapy (S-1 or GEM)					

Data are presented as *n* (%) unless otherwise indicated. *P* values were calculated using Fisher's exact test (categorical variables) or the Kruskal–Wallis test (continuous variables). The *P* value for *KRAS* status was calculated after excluding patients with unknown status, and that for histological type compares adenocarcinoma with other types. Percentages for *KRAS* status were rounded so that each column totals 100%. LD, low dose; ED, equal dose; HD, high dose; ECOG PS, Eastern Cooperative Oncology Group performance status; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; IPMN, intraductal papillary mucinous neoplasm; GEM, gemcitabine; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19 – 9

Characteristic	Total (*n* = 97)	LD (*n* = 12)	ED (*n* = 37)	HD (*n* = 48)	*P* value
Yes	82 (85)	12 (100)	30 (81)	40 (83)	0.33
No	15 (15)	0 (0)	7 (19)	8 (17)	
CEA (ng/mL), median [range]	3.4 [0.9–36.7]	3.2 [1.4–36.7]	3.6 [0.9–10.9]	3.2 [1.3–31.2]	0.40
CA19-9 (U/mL), median [range]	81.0 [1.0–489]	98.5 [1.0–443]	69.0 [1.0–446]	85.5 [1.0–489]	0.68
Body surface area (m^2), median [range]	1.63 [1.29–2.17]	1.85 [1.48–2.17]	1.74 [1.43–1.98]	1.55 [1.29–1.85]	< 0.01
Creatinine clearance (CLcr) (mL/min), median [range]	70.6 [39.7–198.4]	106.7 [72.1–198.4]	85.3 [39.7–145.0]	61.1 [40.5–100.7]	< 0.01

Data are presented as *n* (%) unless otherwise indicated. *P* values were calculated using Fisher's exact test (categorical variables) or the Kruskal–Wallis test (continuous variables). The *P* value for *KRAS* status was calculated after excluding patients with unknown status, and that for histological type compares adenocarcinoma with other types. Percentages for *KRAS* status were rounded so that each column totals 100%. LD, low dose; ED, equal dose; HD, high dose; ECOG PS, Eastern Cooperative Oncology Group performance status; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; IPMN, intraductal papillary mucinous neoplasm; GEM, gemcitabine; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19 − 9

Clinical outcomes

Treatment efficacy and survival

The median follow-up period was 36.7 months (95% confidence interval [CI] 33.6–48.0), median RFS was 36.6 months (95% CI 16.1–NA; NA, not applicable), and median OS was not reached (95% CI 40.7–NA) in all patients (Fig. 1). There were 48 RFS events (49%) and 32 OS events (33%). RFS was significantly longer in the ED group than in the other groups (LD vs. ED, hazard ratio [HR] 3.15, 95% CI 1.28–7.77, *P* = 0.01; HD vs. ED, HR 2.10, 95% CI 1.06–4.13, *P* = 0.03) (Fig. 2). Similarly, OS was significantly shorter in the LD group than in the ED group (HR 2.97, 95% CI 1.04–8.49, *P* = 0.04), whereas there was no significant difference in OS between the HD and ED groups (HR 1.69, 95% CI 0.75–3.79, *P* = 0.21) (Fig. 3).

Response

In all patients, RR was 15.5% (15/97) and DCR was 100% (97/97). RR was 0% in the LD group, 14% in the ED group, and 21% in the HD group, and DCR was 100% in all three groups. The median shrinkage rate of the primary lesion was 12.1% (range − 54.3 to 15.3) in all patients, 5.9% (− 27.2 to 15.3) in the LD group, 12.2% (− 53.4 to 14.9) in the ED group, and 13.1% (− 54.3 to 12.6) in the HD group. The shrinkage rate

was lower in the LD group than in the ED group ($P = 0.06$), whereas there was no significant difference between the ED and HD groups ($P = 0.25$) (Table 2).

Table 2
Response rate, disease control rate, tumor shrinkage rate, and histological response rate

Response, *n* (%)	**All patients (*n* = 97)**	**LD (*n* = 12)**	**ED (*n* = 37)**	**HD (*n* = 48)**	***P* value**
Partial response	15 (15)	0 (0)	5 (14)	10 (21)	
Stable disease	82 (85)	12 (100)	32 (86)	38 (79)	
Response rate	15 (15)	0 (0)	5 (14)	10 (21)	0.24
Disease control rate	97 (100)	12 (100)	37 (100)	48 (100)	1.00
Tumor shrinkage rate, median [range]	−12.1 [− 54.3 to 15.3]	−5.9 [− 27.2 to 15.3]	−12.2 [− 53.4 to 14.9]	−13.1 [− 54.3 to 12.6]	0.02
Histological response, *n* (%)					
Grade 1a	12 (12)	4 (33)	4 (11)	4 (8)	0.07
Grade 1b	62 (64)	7 (58)	22 (60)	33 (69)	0.64
≥ Grade 2	20 (21)	1 (9)	9 (24)	10 (21)	0.57
Not evaluated	3 (3)	0 (0)	2 (5)	1 (2)	0.72

P values were calculated using Fisher's exact test (categorical variables) or the Kruskal–Wallis test (continuous variables). Percentages for histological response were rounded so that each column totals 100%. LD, low dose; ED, equal dose; HD, high dose

Histological grade of therapeutic response

Histological therapeutic effects were grade 1a, grade 1b, grade 2 or higher, and not evaluated in 12%, 64%, 21%, and 3% of all patients, respectively. Grade 1a (mild effect) was observed in 33% of the LD group, 11% of the ED group, and 8% of the HD group, with a trend toward a lower histological therapeutic effect in the LD group than in the ED group ($P = 0.09$) (Table 2).

Adverse events and dosage of chemotherapy

In all patients, the most common grade ≥ 3 AEs were neutropenia (47%), mucositis (9%), febrile neutropenia (4%), and dermatitis (4%). Mucositis was significantly more frequent in the HD group than in the other groups ($P < 0.01$). Dose reduction was performed in 45% of the overall cohort (33% in the LD group, 35% in the ED group, and 56% in the HD group; $P = 0.12$), and treatment discontinuation was required in 10% (0%, 8%, and 15%, respectively; $P = 0.41$) (Table 3). The RDI of S-1 relative to the planned standard dose did not differ significantly among the groups (LD, 82.2%; ED, 80.2%; HD, 76.1%; $P = 0.56$),

nor did the RDI of gemcitabine (LD, 71.6%; ED, 77.6%; HD, 74.1%; *P* = 0.80). In contrast, the BBT-based RDI of S-1 differed significantly among the groups (LD, 65.8%; ED, 75.0%; HD, 104.0%; *P* < 0.01) (Online Resource 2).

Table 3
Incidence of grade 3 or 4 adverse events and dose reduction or discontinuation

Event	**All patients (*n* = 97)**	**LD (*n* = 12)**	**ED (*n* = 37)**	**HD (*n* = 48)**	***P* value**
Grade 3 or 4 adverse events, *n* (%)					
Neutropenia	46 (47)	6 (50)	18 (49)	22 (46)	0.96
Febrile neutropenia	4 (4)	0 (0)	0 (0)	4 (8)	0.18
Mucositis	9 (9)	0 (0)	0 (0)	9 (19)	< 0.01
Dermatitis	4 (4)	0 (0)	1 (3)	3 (6)	0.78
Gastrointestinal disorder	1 (1)	0 (0)	0 (0)	1 (2)	1.00
Non-hematologic disorder	12 (12)	0 (0)	2 (5)	10 (21)	0.06
Dose modification, *n* (%)					
Dose reduction	44 (45)	4 (33)	13 (35)	27 (56)	0.12
Discontinuation	10 (10)	0 (0)	3 (8)	7 (15)	0.41
Reduction or discontinuation	53 (55)	4 (33)	16 (43)	33 (69)	0.02

P values were calculated using Fisher's exact test. LD, low dose; ED, equal dose; HD, high dose

Univariate and multivariate analyses for survival

In the univariate analysis for RFS, CA19-9 < 37 U/mL (HR 0.47, 95% CI 0.24–0.91, *P* = 0.03) and the ED group (HR 0.44, 95% CI 0.23–0.85, *P* = 0.015) were associated with longer RFS, and tumor size ≥ 20 mm with shorter RFS (HR 1.87, 95% CI 1.00–3.49, *P* = 0.049). In the multivariate analysis including these three factors (backward stepwise method), CA19-9 < 37 U/mL (HR 0.47, 95% CI 0.24–0.93, *P* = 0.03) and the ED group (HR 0.45, 95% CI 0.23–0.87, *P* = 0.02) were independent prognostic factors for longer RFS, whereas tumor size was not retained in the final model (HR 1.83, 95% CI 0.97–3.44, *P* = 0.06 at removal). No factor was significantly associated with OS in the univariate analysis, and multivariate analysis for OS was therefore not performed (Table 4).

Table 4
Univariate and multivariate analysis of recurrence-free survival and overall survival

RFS	Univariate analysis				Multivariate analysis			
	HR	**Lower 95% CI**	**Upper 95% CI**	***P* value**	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P* value**
Sex (female vs. male[a])	1.03	0.56	1.90	0.92				
Age (≥ 75 vs. < 75[a])	0.89	0.50	1.58	0.69				
ECOG PS (≥ 1 vs. 0[a])	1.86	0.99	3.48	0.051				
Primary lesion (head vs. body/tail[a])	1.27	0.72	2.26	0.41				
Tumor size (≥ 20 mm vs. < 20 mm[a])	1.87	1.00	3.49	0.049	1.83	0.97	3.44	0.06
Histological response (grade ≥ 2 vs. < 2[a])	0.52	0.22	1.23	0.14				
KRAS (mutant vs. wild type[a])	1.32	0.32	5.48	0.70				
CA19-9 (< 37 vs. ≥ 37 U/mL[a])	0.47	0.24	0.91	0.03	0.47	0.24	0.93	0.03
Histological type (others vs. adenocarcinoma[a])	0.32	0.08	1.34	0.12				
S-1 dose group (ED vs. LD + HD[a])	0.44	0.23	0.85	0.015	0.45	0.23	0.87	0.02
Adjuvant chemotherapy (S-1 vs. none[a])	0.58	0.29	1.17	0.13				

OS	Univariate analysis				Multivariate analysis			
	HR	Lower 95% CI	Upper 95% CI	*P* value	HR	Lower 95% CI	Upper 95% CI	*P* value
Sex (female vs. male[a])	0.98	0.47	2.08	0.97				
Age (≥ 75 vs. < 75[a])	0.76	0.37	1.56	0.46				
ECOG PS (≥ 1 vs. 0[a])	1.59	0.73	3.43	0.24				
Primary lesion (head vs. body/tail[a])	1.51	0.73	3.14	0.27				
Tumor size (≥ 20 mm vs. < 20 mm[a])	1.64	0.76	3.56	0.21				
Histological response (grade ≥ 2 vs. < 2[a])	0.30	0.07	1.26	0.10				
KRAS (mutant vs. wild type[a])	1.65	0.22	12.19	0.63				
CA19-9 (< 37 vs. ≥ 37 U/mL[a])	0.50	0.21	1.15	0.10				
Histological type (others vs. adenocarcinoma[a])	0.28	0.04	2.05	0.21				
S-1 dose group (ED vs. LD + HD[a])	0.53	0.24	1.14	0.10				
Adjuvant chemotherapy (S-1 vs. none[a])	0.51	0.22	1.18	0.12				

[a] Reference category. RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; CA19-9, carbohydrate antigen 19 – 9; ED, equal dose; LD, low dose; HD, high dose. Variables with $P < 0.05$ in the univariate analysis were entered into the multivariate model (backward stepwise method based on the Bayesian information criterion). Multivariate estimates for CA19-9 and S-1 dose group are from the final model; that for tumor size is from the step of its removal. No variable reached $P < 0.05$ for OS, so multivariate analysis was not performed. *KRAS* status was unknown in 14 patients (excluded; $n = 83$)

Discussion

To the best of our knowledge, this is the first study to evaluate the clinical relevance of the BBT formula in patients with RPC receiving NAC-GS. Our main finding was a “U-shaped” relationship between the S-1 dose relative to the BBT-calculated dose and RFS: the ED group, which was expected to achieve the

target AUC, had significantly better RFS than the LD and HD groups. The BBT formula may therefore provide an optimal therapeutic window.

In the LD group, the poor prognosis (median RFS 9.0 months; median OS 25.9 months) was associated with low antitumor efficacy of NAC-GS, indicated by a lower median tumor shrinkage rate (5.9%) and a higher proportion of histological grade 1a responses than in the ED group, suggesting insufficient drug exposure, although the incidence of AEs was also low. These results highlight the importance of maintaining adequate 5-FU concentrations during neoadjuvant therapy for RPC. A substantial proportion of patients in the LD group received adjuvant S-1 at a relatively low dose, suggesting that low-dose S-1 may be insufficient to prevent recurrence even in the adjuvant setting. Furthermore, patients in the LD group were predominantly younger men with a larger BSA and well-preserved renal function. In addition, even at the maximum standard dose of S-1 (120 mg/day) used in real-world NAC-GS, the dose remained insufficient to reach the BBT-recommended dose in almost all patients. Prospective studies are therefore warranted to evaluate whether increasing the S-1 dose beyond the standard maximum can improve clinical outcomes in patients with these characteristics.

Conversely, the shorter RFS in the HD group (19.7 months vs. not reached in the ED group) is a clinical paradox given the relatively high RR (21%). This may be explained by severe toxicity and poor compliance with subsequent treatment. The HD group had a markedly higher incidence of grade ≥ 3 mucositis (19%, $P < 0.01$), and 69% of patients required treatment modification (dose reduction or discontinuation). Frequent interruptions and premature discontinuation of NAC may allow tumor regrowth during drug-free intervals. Severe mucositis can also impair nutritional status and general condition, potentially compromising tolerance of surgery and postoperative adjuvant therapy. In advanced pancreatic cancer, baseline nutritional status and quality of life have been reported to affect the maintenance of adequate dose intensity and survival [15]. Moreover, an exploratory analysis of the JASPAC-01 trial of adjuvant S-1 for RPC reported that the overdose group had a higher incidence of anemia and a significantly increased risk of dose reduction [16], consistent with our findings in NAC-GS. Avoiding overdose by applying the BBT formula is therefore critical for optimizing the therapeutic index of NAC-GS. These results are also consistent with a pooled analysis of the SPIRITS and G-SOX trials in gastric cancer by Booka et al., in which the HD group had a significantly higher incidence of neutropenia than the ED group and the LD group tended to have shorter OS [10].

Conventional S-1 dosing relies solely on BSA, which overlooks individual variation in renal function, a primary determinant of gimeracil clearance. This frequently leads to unpredictable toxicity in patients with impaired renal function and subtherapeutic exposure in those with a large BSA and good renal function. Compared with conventional BSA-based RDI, BBT-based RDI is a more dose-correlated metric, suggesting superior clinical utility.

Although the Prep-02/JSAP-05 trial established the efficacy of NAC-GS for RPC [2], balancing safety and efficacy remains a challenge. Our findings demonstrated that the BBT formula is an easily available tool

for identifying the “sweet spot” of S-1 dosing, maximizing therapeutic efficacy while minimizing debilitating toxicity.

This study has some limitations. First, it was a retrospective, single-center study with a relatively small sample size, particularly in the LD group (n = 12), which could introduce selection bias in patient recruitment and information bias in data extraction from medical records. Second, potential confounding due to physician bias in determining dose-reduction criteria could not be entirely ruled out. Third, the number of events was limited (48 for RFS and 32 for OS), which restricted the power of the survival analyses, particularly for OS.

Based on this retrospective analysis, S-1 dose optimization using the BBT formula appears to be beneficial even in NAC-GS therapy for RPC. A phase I/II trial is ongoing to evaluate the safety and efficacy of S-1, oxaliplatin, and nivolumab combination therapy with a BBT formula-based optimal S-1 dose for HER2-negative unresectable, advanced, or recurrent gastric cancer (jRCTs031230127), and we plan a multicenter prospective study to evaluate the clinical utility of the BBT formula in perioperative chemotherapy for RPC.

Managing the S-1 dose using the BBT formula is clinically useful for enhancing the safety profile of NAC-GS and maximizing RFS in patients with RPC. Future prospective multicenter studies are warranted to validate these findings and firmly establish BBT-based dosing in this patient population.

Declarations

Conflict of interest

Narikazu Boku has received honoraria from Astellas, Bristol Myers Squibb, and Taiho and research funding from Pfizer. The other authors have no conflicts of interest to declare.

Ethics approval

All procedures performed in this study involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the institutional review board of The University of Tokyo Hospital (Approval No. 2058).

Consent to participate

The study protocol was described on the hospital website, and participants were provided with the opportunity to opt out. No additional informed consent was obtained from the enrolled patients.

Consent to publish

Not applicable.

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Author contributions

Conception and design: KF, KI, and KN; acquisition of data: KF, KI, and KN; analysis and interpretation of data: KF, KI, KN, and NT; drafting, review, and/or revision of the manuscript: all authors; administrative, technical, or material support: KF, KI, and KN; study supervision: NB and MF.

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Data availability

The data that support the findings of this study are not openly available for reasons of sensitivity but are available from the corresponding author upon reasonable request. Data were deposited in a controlled access data storage at The University of Tokyo Hospital.

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Figures

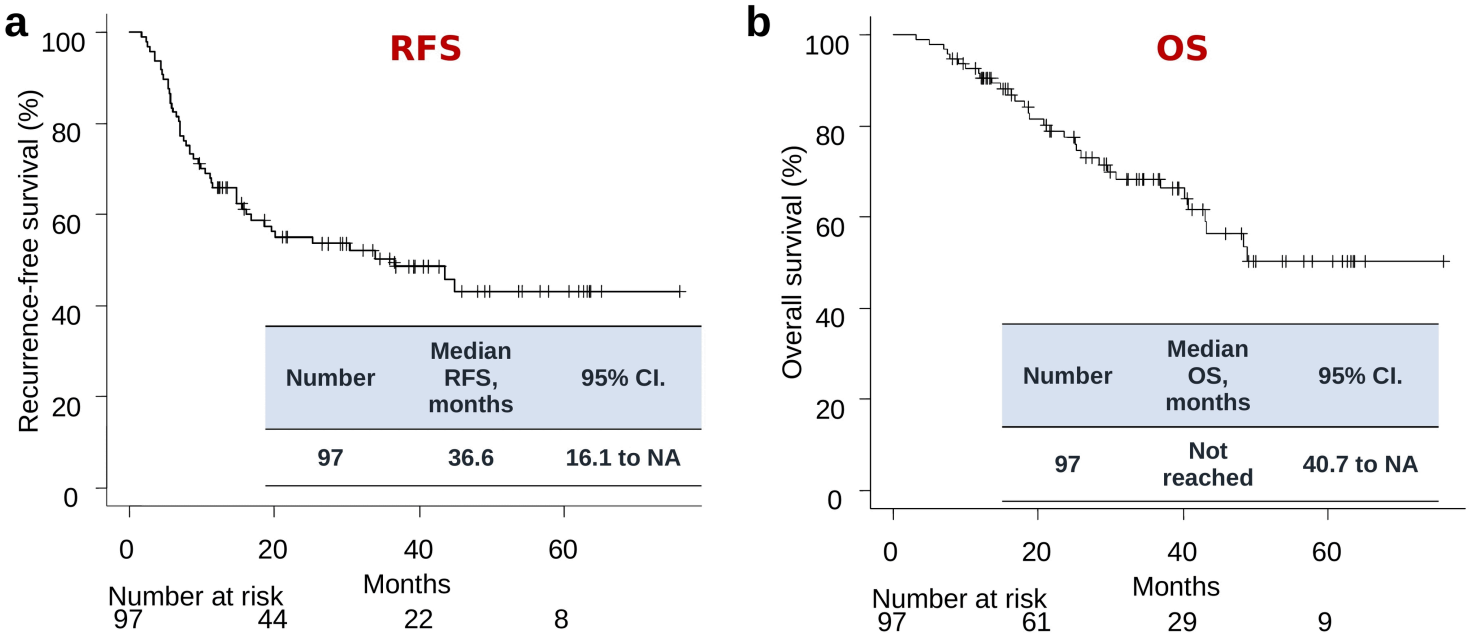
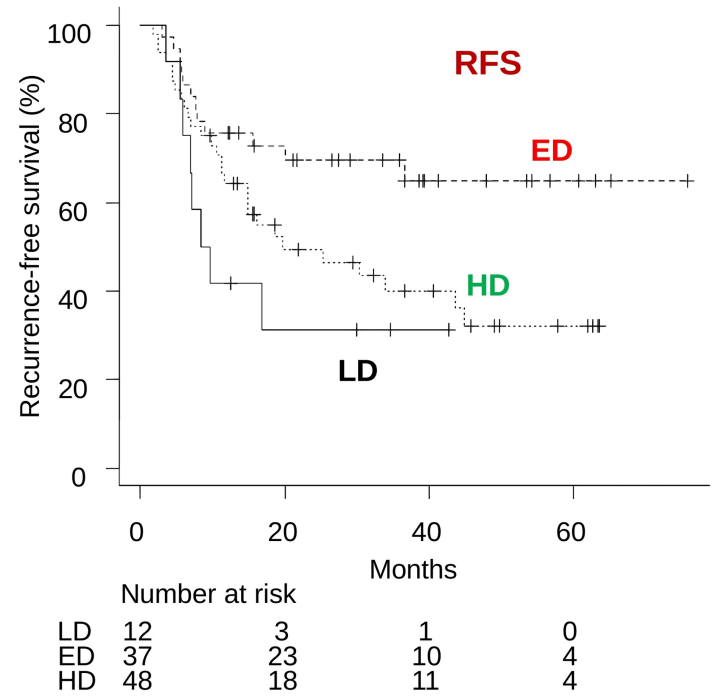


Figure 1

Recurrence-free survival (a) and overall survival (b) of patients with resectable pancreatic cancer treated with neoadjuvant gemcitabine plus S-1 combination therapy (NAC-GS). RFS, recurrence-free survival; OS, overall survival; CI, confidence interval; NA, not applicable

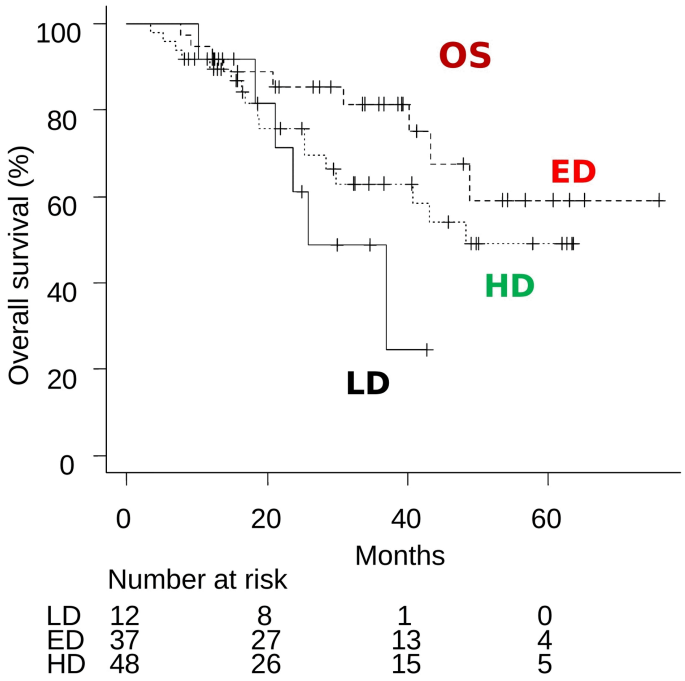


Dose	N	Median RFS, months (95% CI)	HR (95% CI, *P*)
LD	12	9.0 (5.4 to NA)	3.15 (1.28 to 7.77); *P* = 0.013
ED	37	NA (36.6 to NA)	Reference
HD	48	19.7 (11.6 to 44.9)	2.10 (1.06 to 4.13) *P* = 0.032

Figure 2

Association between S-1 dose (HD vs. ED vs. LD group) and recurrence-free survival in patients with resectable pancreatic cancer treated with NAC-GS. RFS, recurrence-free survival; HD, high dose; ED, equal

dose; LD, low dose; HR, hazard ratio; CI, confidence interval; NAC-GS, neoadjuvant gemcitabine plus S-1 combination therapy; NA, not applicable



Dose	N	Median OS, months (95% CI)	HR (95% CI, *P*)
LD	12	25.9 (18.2 to NA)	2.97 (1.04 to 8.49); *P* = 0.043
ED	37	NA (43.2 to NA)	Reference
HD	48	48.3 (28.4 to NA)	1.69 (0.75 to 3.79) *P* = 0.21

Figure 3

Association between S-1 dose (HD vs. ED vs. LD group) and overall survival in patients with resectable pancreatic cancer treated with NAC-GS. OS, overall survival; HD, high dose; ED, equal dose; LD, low dose; HR, hazard ratio; CI, confidence interval; NAC-GS, neoadjuvant gemcitabine plus S-1 combination therapy; NA, not applicable

Supplementary Files

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