

A Pilot Study- Neoadjuvant Chemotherapy with Gemcitabine and S1 in Patients with Resectable and Borderline Resectable Pancreatic Cancer

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Abstract

Introduction: Combination chemotherapy with gemcitabine and S-1 (GS) in metastatic advanced pancreatic cancer patients is superior to gemcitabine alone in response rate and progression free survival. We investigated this combination chemotherapy as neoadjuvant therapy for resectable and borderline resectable pancreatic cancer.

Methods: Eleven patients with resectable or borderline resectable pancreatic cancer were administered to neoadjuvant chemotherapy with GS (NeoGS) from June 2011 to March 2013 at Nippon Medical School, and short-term outcome was evaluated.

Results: The median age was 69.1 years. According to NCCN criteria, 6 patients were resectable diseases and 5 were borderline resectable diseases. All patients received Neo GS with a median cycle of 3.5 (range: 2-11). No serious adverse events including death or life-threatening complications happened. Grade 3 or 4 chemotherapy-related toxicities included neutropenia (81.8%), anemia (18.2%), thrombocytopenia (18.2%), and febrile neutropenia (9.1%). Other non-hematological toxicities with grade 1 or 2 were anorexia (36.4%), constipation (36%), nausea (27.3%), diarrhea (18.2%), dysgeusia (9.1%), and stomatitis (9.1%). Radiologically, partial response was documented in 3 patients (27.3%), and the remaining 8 patients (72.7%) had stable disease. All patients underwent pancreatic resection with lymphadenectomy. An R0 resection was achieved in 10 of 11 (90.9%), and negative nodal involvement (N0) was found in 6 (54.5%). Pathologically, all specimens showed at least Evans grade I, while eight of eleven (72.7%) had Evans grade IIa. There was no mortality and severe morbidity including clinically relevant pancreatic fistula. All patients received adjuvant chemotherapy with either gemcitabine or S1.

Conclusion: This pilot study suggests NeoGS is feasible in patients with resectable and borderline resectable pancreatic cancer and may be associated with a high R0 resection rate and a low lymph node metastasis rate, suggesting that further phase 2 and 3 trials are warranted.

Keywords: Resectable and borderline resectable pancreatic cancer; Neoadjuvant chemotherapy; Gemcitabine; S-1; Gemcitabine+S-1

Introduction

Pancreatic cancer is a 5th leading cause of cancer death and causes approximately 28,800 deaths per year in Japan [1]. Pancreatic cancer has an extremely poor prognosis with a 5-year overall survival of less than 5% [2]. Pancreatic resection remains the only hope for long-term survival, but unfortunately only 15- 20% of patients with pancreatic cancer are capable of undergoing pancreatic resection [3]. To improve the survival of patients with pancreatic cancer, increasing rate of resection with negative surgical margins (R0 resection) and decreasing rate of metastatic Lymph Nodes (LN) are important [3]. Recently, randomized control trials demonstrated adjuvant chemotherapy with gemcitabine after curative resection of pancreatic cancer significantly prolonged disease free survival compared with surgery alone but did not significantly prolonged overall survival [4,5]. The major problem of adjuvant chemotherapy is that a large proportion of patients cannot receive any treatment due to preoperative morbidity after pancreatic resection [6].

On the contrary, neoadjuvant treatment can be applied to almost all patients since it is independent of the perioperative morbidity. In fact, several randomized phase 2 trials in resectable pancreatic cancer demonstrated that neoadjuvant chemotherapy with gemcitabine and cisplatin was associated with a higher resection rate and a favorable survival rate [7,8]. S-1 is a fourth generation oral fluoropyrimidine, which combines tegafur with two 5-fluorouracil modulators, gimeracil, which is a 200-fold more potent inhibitor of dihydropyrimidine

dehydrogenase than uracil and potassium oxonate, which can reduce the diarrhea caused by Tegafur at a molar ratio of 1 to 0.4 to 1 (Tegafur: gimeracil: potassium oxonate) [9]. A phase 2 trial of S-1 for advanced metastatic pancreatic cancer have shown a response rate of 37.5% and the median time to progression and the overall survival time were 3.7 months and 9.2 months [10]. Moreover, multicenter randomized phase 2 trials of a combination of gemcitabine and S-1 (GS) for advanced metastatic pancreatic cancer showed the significant superiority of GS in response rate and progression free survival, but not in overall survival when compared to gemcitabine alone [11,12]. GS as neoadjuvant therapy in patients with resectable or borderline resectable pancreatic cancer may be effective with respect to progression and survival.

However, a trial of neoadjuvant chemotherapy with gemcitabine and S-1 (NeoGS) for resectable and borderline resectable pancreatic cancer has not been demonstrated. Therefore, we conducted a pilot

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study of NeoGS for patients with resectable and borderline resectable pancreatic cancer.

Patients and Methods

Patients

Between June 2011 and March 2013, 11 patients who were diagnosed as histologically or cytologically proven resectable or borderline resectable pancreatic adenocarcinoma with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ function at Nippon Medical School were included. All patients were planned to perform neoadjuvant chemotherapy with GS followed by surgery as anti-cancer treatment. A written informed consent was obtained from all patients.

Staging and resectability criteria

Contrast-enhanced (CE) CT scan of chest and abdomen ruled out distant metastases. Positron-emission tomography (PET) CT was also used for detecting unexpected distant metastases, if available. Local resectability was assessed by relationship between tumor extent and major visceral vessels, including Superior Mesenteric Artery (SMA), Celiac Artery (CA), Common Hepatic Artery (CHA), and Portal Vein (PV) or superior mesenteric vein (SMV), based on the CECT. We applied the National Comprehensive Cancer Network (NCCN) Guidelines criteria for definition of resectable or borderline resectable pancreatic cancer [13,14]. These criteria are summarized in Table 1.

Neoadjuvant and adjuvant chemotherapy

Neoadjuvant chemotherapy consists of 1,000 mg/m² gemcitabine given as an intravenous infusion over 30 min on day1 and day8, and 30mg/m² S1 given orally twice daily on days 1 to 14, every 3 weeks. Patients with resectable pancreatic cancer received 2 cycles and patients with borderline resectable pancreatic cancer received more than 2 cycles.

After pancreatic resection, patients received adjuvant chemotherapy with 1000mg/m² gemcitabine on day1, day8, and day15 every 4 weeks or 40mg/m² S1 twice daily on days 1 to 28, every 6 weeks for 6 months.

Surgery

Surgery was performed within 10-30 days after the last neoadjuvant chemotherapy. All patients underwent pancreatic resection with lymphadenectomy. In cases with suspected tumor infiltration into the PV and/or SMV, concomitant resection of those veins with reconstruction was performed. The operation was defined as an R0 resection if there was no microscopic tumor found at the margin and as an R1 resection if a margin was microscopically positive.

Response and toxicity assessments and perioperative complications

Tumor responses were measured by CECT or magnetic resonance imaging scans by comparing between the baseline and after neoadjuvant chemotherapy according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. Adverse events during chemotherapy were graded by the "Common Terminology Criteria for Adverse Events" version 4.0. The International Study Group on Pancreatic Fistula Definition defined pancreatic fistula [15].

Pathologic response

To assess the pathologic effects of neoadjuvant chemotherapy,

the grading system reported by Evans et al. was used [16]. Briefly, the Evans grading system consists of scale from I to IV based on the degree of cytological change and tumor destruction as follows: grade I refers to characteristic cytologic changes of malignant cells are present, but little (below 10%) or no tumor cell destruction is evident; grade IIa, destruction of 10 to 50% of tumor cells; grade IIb, destruction of 51 to 90% of tumor cells; grade III, few (below 10%) viable-appearing tumor cells present; grade IV, no viable tumor cells are present.

Results

Patient's characteristics

From June 2011 and March 2013, 11 patients (9 males and 2 females) were diagnosed as resectable or borderline resectable pancreatic cancer, and received neoadjuvant chemotherapy with gemcitabine and S1. The baseline characteristics of these patients are summarized in Table 2. According to the NCCN criteria, 6 patients had resectable diseases and 5 patients had borderline resectable diseases. Of those who had borderline disease, three patients had abutment or encasement of the SMV, one had abutment of the SMA, and one had both encasement of the SMV and abutment of the SMA (Figures 1a and 1b).

Category	Criteria
Resectable	No distant metastases No evidence of SMV and portal vein abutment, distortion, tumor thrombus or venous encasement Clear fat planes around the celiac axis, hepatic artery, and SMA.
Borderline resectable	No distant metastases Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction. Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis. Tumor abutment of the SMA not to exceed 180 degrees of the circumference of the vessel wall

Abbreviations: SMA- Superior Mesenteric Artery; SMV- Superior Mesenteric Vein

Table 1: Criteria used for determining local resectability for pancreatic cancer.

Characteristic	Number	%
Age at diagnosis, yr Median(range)	69.1(59~78)	
Sex		
Male	9	81.8
Female	2	18.2
ECOG Performance status	10	90.9
0		
1	1	9.1
Site of tumor		
Head	10	90.9
Tail	1	9.1
Resectability	6	54.5
Resectable	3	27.3
Borderline resectable		
SMV encased (short segment)	1	9.1
SMA abutment		
SMA abutment and SMV encased	1	9.1

Abbreviations: SMV- Superior Mesenteric Vein; SMA- Superior Mesenteric Artery

Table 2: Patient characteristics, n=11.

Toxicity and adverse events

All 11 patients received adequate neoadjuvant therapy with gemcitabine and S1 with a median cycle of 3.5 (range: 2-11). No serious

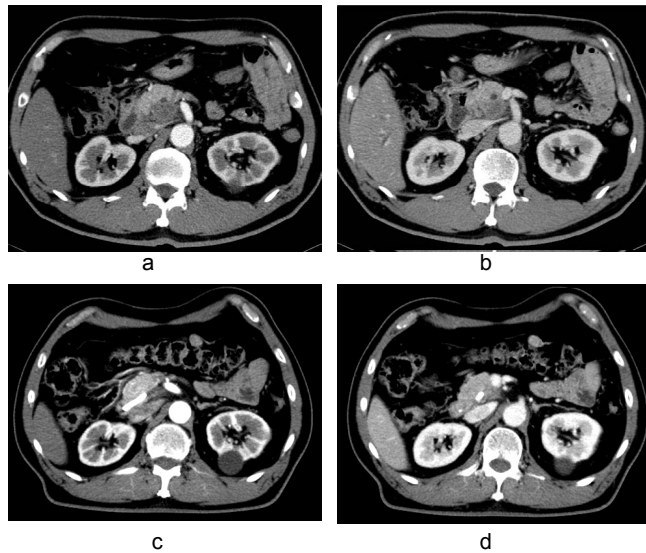


Figure 1: A 64-year-old man was diagnosed with pancreatic head cancer. The SMA abutment and the SMV involvement were detected in CECT (a, b). He was diagnosed as borderline resectable according to NCCN criteria. After 3 cycles of neoadjuvant chemotherapy with gemcitabine and S1, The tumor at pancreas head had regressed, and SMA abutment were improved but SMV encasement still existed in CECT(c, d) (partial response). He underwent laparoscopic subtotal stomach preserving Pancreaticoduodenectomy with lymphadenectomy and the SMV resection. The operation was R0 resection and the pathologic stage was T1N0 (case 9).

	Grade 3 or 4	%
Neutropenia	9	81.8
Anemia	2	18.2
Thrombocytopenia	2	18.2
Febrile neutropenia	1	9.1

Other non-hematological toxicities with grade 1 or 2 were anorexia (36.4%), constipation (36%), nausea (27.3%), diarrhea (18.2%), dysgeusia (9.1%), and stomatitis (9.1%).

Table 3: Grade3 or 4 adverse events associated with gemcitabine and S1 neoadjuvant therapy.

Patient	Clinical T stage	Clinical N stage	Site	Criteria	Factor	No. of cycle	RECIST response	Surgery	Pathologic T stage	Pathologic N stage	Pathologic response	Surgical margin
1	4	1	H	BR	SMA	4	SD	SSPPD	3	1	Ila	R0
2	3	0	H	BR	SMV	4	PR	SSPPD/SMVR	3	0	Ila	R0
3	1	0	H	R	-	2	SD	SSPPD	1	0	I	R0
4	3	0	H	R	-	2	SD	SSPPD	3	1	I	R0
5	3	0	H	BR	SMV	2	SD	SSPPD/SMVR	3	0	I	R0
6	3	1	T	R	-	11	PR	DP	3	1	Ila	R0
7	3	0	H	R	-	2	SD	Lap-PD	3	1	Ila	R0
8	3	0	H	R	-	2	SD	Lap-SSPPD	3	0	Ila	R1
9	4	0	H	BR	SMV/SMA	3	PR	Lap-SSPPD/SMVR	1	0	Ila	R0
10	3	0	H	BR	SMV	4	SD	Lap-SSPPD/SMVR	3	1	Ila	R0
11	3	0	H	R	-	2	SD	Lap-SSPPD	3	0	Ila	R0

Abbreviations: RECIST- Response Evaluation Criteria In Solid Tumors; H- Head of Pancreas; T- Tail of Pancreas; SMA- Superior Mesenteric Artery; SMV- Superior Mesenteric Vein; SD- Stable Disease; PR- Partial Response; SSPPD- Subtotal Stomach Preserving Pancreaticoduodenectomy; SMVR- Superior Mesenteric Vein Resection; DP- Distal Pancreatectomy; Lap-PD- Laparoscopic Pancreaticoduodenectomy; Lap-SSPPD- Laparoscopic Subtotal Stomach Preserving Pancreaticoduodenectomy

Table 4: Clinical characteristics of patients who underwent pancreatic resection after neoadjuvant chemotherapy with gemcitabine and S1.

adverse events including death or life-threatening complications happened. As shown in Table 3, most common hematological toxicities with grade 3 or 4 were neutropenia (81.8%), anemia (18.2%), thrombocytopenia (18.2%), and febrile neutropenia (9.1%). Other non-hematological toxicities with grade 1 or 2 were anorexia (36.4%), constipation (36.4%), nausea (27.3%), diarrhea (18.2%), dysgeusia (9.1%), and stomatitis (9.1%).

Radiologic tumor response

None of the patients showed an increase in tumor size during NeoGS on CECT. Partial response was documented in 3 patients (27.3%, Figures 1c and 1d), and the remaining 8 patients had stable disease (72.7%) (Table 4).

Surgical outcome

After radiologic reevaluation using CECT, all patients were deemed resectable or borderline resectable after neoadjuvant therapy. All patients underwent pancreatic resection with lymphadenectomy. The R0 resection rate was 90.9% (10 patients) and R1 resection rate was 9.1% (1 patient) (Table 4). None of patients had perioperative death and severe postoperative morbidities including pancreatic fistula graded B or C.

Pathologic response

Histopathologic assessment of the resected specimen in the 11 patients who received NeoGS is summarized in Table 4. Most of the pancreatic tumors located in the head of the pancreas (N=10; 90.0%). Most of the patients had T3N1M0 tumors (N=5; 45.5%). Negative lymph node metastasis was found in 6 patients (54.5%). With respect to pathologic response, minimal response was present in 8 patients (grade IIa: N=8; 72.7%).

Discussion

Recently, results of a large randomized phase 3 trial of GS and gemcitabine alone in unresectable pancreatic cancer patients, known as the GEST trial, were reported. This large-scale (N>600) trial demonstrated significant superiority of GS in response rate and progression free survival but not in overall survival when compared to gemcitabine alone [17].

The current pilot study evaluated the feasibility and initial therapeutic effect of NeoGS in resectable and borderline resectable pancreatic cancer patients. The patients who received NeoGS had

Year	Author	Patients	Borderline N (%)	Chemotherapy	Radiation (Gy)	Resection rate N(%)	R0 resection N(%)	Negative LN metastasis: N(%)	Median overall survival(M)
2007	Palmer [7]	24	-	Gem	-	8(37.5%)	6(75%)	2(25%)	9.9
		26	-	Gem, Cis	-	18(69.2%)	12(46.2%)	7(44%)	15.6
2008	Heinrich [8]	28	-	Gem, Cis	-	25(89.3%)	20(80%)	-	19.1
2008	Varadhachary [18]	90	-	Gem, Cis	30	52(58%)	50(96.2%)	20(38.5%)	31
2009	Turrini [19]	102	-	5FU, Cis	45	62(60.8%)	57(91.9%)	47(75.8%)	23
2011	Patel [20]	17	17(100%)	Gem, TXT, Cap	50 (5FU)	9(64%)	8(88.9%)	-	15.6
2011	Sahora [21]	33	15(45.5%)	Gem, Ox	-	13(39%)	9(69.2%)	4(30.8%)	22
2012	Lee [22]	43	18(41.9%)	Gem, Cap	-	17(39.5%)	14(82.4%)	7(41.2%)	23.1
2012	Hosein [23]	18	4(23%)	FOLFIRINOX	-	9(50%)	8(88.9%)	-	-
	This study	11	5(45.5%)	Gem, S1	-	11(100%)	10(90.9%)	6(54.5%)	-

Abbreviations: LN- Lymph Node; Gem- Gemcitabine; Cis- Cisplatin; TXT- Docetaxel; Cap- Capecitabine; Ox- Oxaliplatin; M- Month

Table 5: Neoadjuvant chemotherapy in resectable and borderline resectable pancreatic cancer.

neither death nor life-threatening serious adverse events, but most of the patients had neutropenia or other hematological toxicities with grade 3 or 4. NeoGS in patients with resectable and borderline resectable pancreatic cancer resulted in an R0 resection rate of 90.9% with a negative lymph node metastasis rate of 54.5%.

Some neoadjuvant chemotherapy regimens for resectable or borderline resectable pancreatic cancer are reported. As summarized in Table 5, those regimens were gemcitabine alone, gemcitabine plus cisplatin, 5FU plus cisplatin, gemcitabine plus oxaliplatin, gemcitabine, docetaxel plus capecitabine, gemcitabine plus capecitabine, and FOLFIRINOX [18-23]. The FOLFIRINOX regimen consists of 5-fluorouracil, leucovorin, irinotecan and oxaliplatin. The randomized phase 3 trial demonstrated FOLFIRINOX in patients with metastatic pancreatic cancer was significantly superior to gemcitabine alone in response rate, progression free survival and overall survival [24]. Most of all regimens were based on combination chemotherapy with gemcitabine. Although the patient characteristics of those studies were different in resectability criteria, in combination chemotherapies, R0 resection rates were reported with a range from 66.7% to 96.2%, and negative lymph node metastasis rates were from 30.8% to 75.8%. In this study, R0 resection rate and negative lymph node rate were similar to those of other combination chemotherapies. Although Neo GS showed a high R0 resection rate and a low lymph node metastasis rate in resectable and borderline resectable pancreatic cancer, the findings of pathological response was limited.

In conclusion, this pilot study suggests that NeoGS is feasible in patients with resectable and borderline resectable pancreatic cancer and may be associated with a high R0 resection rate and a low lymph node metastasis rate. Randomized phase 2 and 3 trials of NeoGS in patients with resectable or borderline resectable pancreatic cancer are warranted for making sure if NeoGS would prolong survival for patients with resectable and borderline resectable pancreatic cancer.

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