プロトコール治療開始できなかった症例

登録番号	割付群	中止理由	詳細
007-04-N	試験群	患者からの中止の申し出(有害事象と関係なし)	同意取得後に、同意撤回の申し出があった。
025-13-N	試験群	患者からの中止の申し出(有害事象と関係なし)	患者より、親族のいる関西で治療希望の申し出あり、他院へ。登録日以降、受診なく、電話で中止の申し出。
044-07-N	試験群	患者からの中止の申し出(有害事象と関係なし)	早期手術を希望された。

プロトコール治療中止理由の詳細(増悪、再発、転移以外)

登録番号	中止時期	中止理由	詳細
008-22-N	手術したがS-1開始できず中止	術後10週以内に投与開始基準を満たさず、S-1を開始で	術前GSでの副作用(重篤な皮膚障害)のため
034-26-N	手術したがS-1開始できず中止	術後10週以内に投与開始基準を満たさず、S-1を開始で	術後腸閉塞で再手術を行い、回復が間に合わなかった
036-04-S	手術したがS-1開始できず中止	術後10週以内に投与開始基準を満たさず、S-1を開始で	術後合併症による。
075-22-S	手術したがS-1開始できず中止	術後10週以内に投与開始基準を満たさず、S-1を開始で	投与開始直前にヘルペスを発症したため
015-22-N	手術したがS-1開始できず中止	術後10週以内に投与開始基準を満たさず、S-1を開始できず+その他	術前に好酸球性肺炎の像がありS-1のDLST試験を行った結果陽性であったためS-1投与不能と判断
047-22-N	手術したがS-1開始できず中止	患者からの中止の申し出(有害事象と関係なし)	術前のGS療法がきつかったため拒否
078-20-S	手術したがS-1開始できず中止	転居、転院、多忙などにより継続的な診察が困難	S-1術後補助療法開始前に、交通事故により他院に入院。他院にてS-1療法を行うことになった。
049-49-N	手術したがS-1開始できず中止	その他	術後合併症によりADLの低下を認め、近医に転院しての加療を要した。また、併存する尿管結石に対しても近医での手術を要し、その治療を優先させる必要があった。
023-23-N	手術したがS-1開始できず中止	画像検査で転移・再発を確認+その他	術後補助化学療法開始前に下痢で受診。その際のCTで多発肝転移を指摘された為、プロトコール中止となりました。
016-03-S	手術したがS-1開始できず中止	切除標本の病理組織検査で通常型膵癌以外だった	自己免疫性膵炎
056-22-S	手術したがS-1開始できず中止	切除標本の病理組織検査で通常型膵癌以外だった	病理でIPMCであった
062-22-S	手術したがS-1開始できず中止	切除標本の病理組織検査で通常型膵癌以外だった	病理でIPMCとの診断であった。
080-42-S	手術したがS-1開始できず中止	切除標本の病理組織検査で通常型膵癌以外だった	下部胆管癌と診断された
054-01-S	S-1開始したが途中で中止	その他	TS-1内服後の食欲不振強く連日の内服は困難と判断。(ADL全身状態より判断)。9/30～TS-1100mg/day隔日投与に変更し、現在も加療継続中。
055-23-N	S-1開始したが途中で中止	その他	followCTで肺塞栓、DVT指摘され、WF導入の為、TS-1中止した。
063-41-S	S-1開始したが途中で中止	その他	全身状態悪化
010-01-N	S-1開始したが途中で中止	2コース以降において、前コース最終内服日より4週を超えても投与再開できず	血液毒性(1コース最終内服(8/23)以後、WBC低下あり、10/4再開基準満たさずプロトコールoffとなる)
027-41-S	S-1開始したが途中で中止	S-1を用量レベルで投与中に減量基準に該当する有害事象が出現	大腸炎(偽膜性腸炎)Grade3
086-11-S	S-1開始したが途中で中止	S-1を用量レベルで投与中に減量基準に該当する有害事象が出現	血小板減少Grade3

重篤な有害事象

■急送報告義務のある有害事象 ・・・ なし
・プロトコール治療中または最終プロトコール治療日から30日以内の全ての死亡(因果関係を問わない)
・予期されないGrade4の非血液毒性
・予期されないClavien分類GradeIV以上(ICU管理を要する)の周術期合併症

■通常報告義務のある有害事象 ・・・ 4 件
・最終プロトコール治療から31日以降で、プロトコール治療との因果関係が否定できない死亡
・予期されるGrade4の非血液毒性
・予期されないGrade2、Grade3の有害事象
・その他重大な医学的事象
(化学療法中の入院加療を要する有害事象、永続的または顕著な障害、その他、研究グループ全施設で共有すべきと思われるもの)

登録番号	有害事象発生日	有害事象名	Grade	因果関係が疑われる治療・薬剤	試験治療との因果関係	予期	転帰	死亡との因果関係	詳細	効果・安全性評価委員会の検討結果
008-22-N	2013/4/18	口腔粘膜炎、 斑状丘疹状皮疹	3 2	TS-1、GEM	あり	される	軽快	—	2013/4/8 GS療法開始。 4/15 GEM 2投目、S-1開始したが、翌日から口内炎Grade3、発疹Grade3、食欲不振Grade3にてS-1休薬。 4/18 発熱(38度程度)、丘疹状皮疹出現し入院。 4/23 GS療法終了決定。 5/16 手術。	継続可、プロトコール変更不要
010-01-N	2013/6/18	術中尿路損傷	3	手術、術前化学療法	あり(手術) なし(GS)		不変	—	2013/4/5 GS療法開始(GEM2回投与) 5/30 手術(膵頭十二指腸切除) 6/6頃より背部痛が出現、6/13CTにより、後腹膜腔に嚢胞状構造物を同定。 6/18 CTガイド下穿刺術により、5/30の術中操作に伴う右尿管離断と診断。 6/21 腎瘻造設術を施行。今後再手術の可能性がある。	継続可、プロトコール変更不要
027-41-S	2013/9/4	大腸炎(偽膜性腸炎)	3	TS-1	あり	される	軽快	—	2013/6/4 膵頭十二指腸切除術、合併切除臓器なし、術後合併症あり 膵瘻ISGPF <B:臨床症状・処置を伴う>, 麻痺性イレウス(Grade2) 7/9 S-1単独療法開始(120mg/日) 1コース中下痢はGrade0 7/16 術後退院 8/21 2コース目開始(Ccr117ml/min) 9/4 高度の下痢(Grade3)にて入院(S-1休止)。偽膜性腸炎と診断し、バンコマイシン内服開始 10/3 プロトコール治療中止	継続可、プロトコール変更不要
074-10-N	2014/1/9	四肢浮腫	3	TS-1、手術	あり (いずれと因果関係があるかは不明)	される	軽快	—	2013/8/5～9/8 GS療法は問題なく完了(GEM1000mg/m2、S-1 80mg/日) 9/24 膵全摘出術、合併切除臓器、術後合併症 なし、 10/31退院 11/28より術後補助療法1コース目(100mg/日)開始。12/26の定期受診時、下肢浮腫(Grade1)を認めた。2週間休薬の後、2014/1/9受診、四肢浮腫(Grade3)を認め入院、利尿剤治療を開始した。2コース開始は延期中。	継続可、プロトコール変更不要

GS療法開始前Grade頻度(試験群のみ)

臨床検査値

項目	G0	G1	G2	G3	G4	N	G1≤	G3-4 (%)	G4 (%)
白血球数減少	39	3	0	0	0	42	3	0	0
好中球数減少	41	1	0	0	0	42	1	0	0
貧血(ヘモグロビン減少)	29	12	1	0	0	42	13	0	0
血小板数減少	38	4	0	0	0	42	4	0	0
AST増加	34	8	0	0	0	42	8	0	0
ALT増加	24	16	2	0	0	42	18	0	0
ALP増加	24	16	2	0	0	42	18	0	0
総ビリルビン増加	36	2	4	0	0	42	6	0	0
クレアチニン増加	40	2	0	0	0	42	2	0	0
低アルブミン血症	24	16	0	0	0	40	16	0	0
低Na血症	42	0	-	0	0	42	0	0	0
高Na血症	38	3	0	1	0	42	4	2.4	0
低K血症	41	1	-	0	0	42	1	0	0
高K血症	42	0	0	0	0	42	0	0	0

項目	G0	G1	G2	G3	G4	N	G1≤	G3-4 (%)	G4 (%)
発熱	42	0	0	0	0	42	0	0	0
発熱性好中球減少症	42	0	0	0	0	42	0	0	0
口腔粘膜炎	42	0	0	0	0	42	0	0	0
下痢	42	0	0	0	0	42	0	0	0
悪心	42	0	0	0	-	42	0	0	-
嘔吐	42	0	0	0	0	42	0	0	0
疲労	41	1	0	0	-	42	1	0	-
食欲不振	40	2	0	0	0	42	2	0	0
斑状丘疹状皮疹(発疹)	42	0	0	0	-	42	0	0	-

GS療法中の最悪Grade頻度(試験群のみ)

臨床検査値　　42 例(GS療法の症例報告書受領済み)

項目	G0	G1	G2	G3	G4	N	G1≤	G3-4 (%)	G4 (%)
白血球数減少	4	10	17	8	3	42	38	26.19	7.14
好中球数減少	1	3	12	15	11	42	41	61.90	26.19
貧血(ヘモグロビン減少)	1	28	12	1	0	42	41	2.38	0
血小板数減少	8	21	9	2	2	42	34	9.52	4.76
AST増加	23	16	1	2	0	42	19	4.76	0
ALT増加	19	18	3	2	0	42	23	4.76	0
ALP増加	24	14	3	1	0	42	18	2.38	0
総ビリルビン増加	29	3	8	2	0	42	13	4.76	0
クレアチニン増加	36	6	0	0	0	42	6	0	0
低アルブミン血症	11	22	9	0	0	42	31	0	0
低Na血症	42	0	–	0	0	42	0	0	0
高Na血症	26	13	0	3	0	42	16	7.14	0
低K血症	38	4	–	0	0	42	4	0	0
高K血症	36	5	0	1	0	42	6	2.38	0

項目	G0	G1	G2	G3	G4	N	G1≤	G3-4 (%)	G4 (%)
発熱	33	6	3	0	0	42	9	0	0
発熱性好中球減少症	38	0	0	4	0	42	4	0.10	0
口腔粘膜炎	30	5	4	3	0	42	12	0.07	0
下痢	36	5	0	1	0	42	6	0.02	0
悪心	33	9	0	0	–	42	9	0	–
嘔吐	41	1	0	0	0	42	1	0	0
疲労	31	9	1	1	–	42	11	0.02	–
食欲不振	30	9	0	3	0	42	12	0.07	0
斑状丘疹状皮疹(発疹)	24	8	5	5	–	42	18	0.12	–

規定項目以外の有害事象　　42例を分母として

項目	G0	G1	G2	G3	G4	N	G1≤	G3-4 (%)	G4 (%)
胆管炎		–	2	0	0		2	0	0
腸炎		1	0	1	0		2	0.02	0
便秘		1	0	0	0		1	0	0
頭痛		1	0	0	0		1	0	0
脱毛症		1	1	–	–		2	0	0
色素沈着		2	0	–	–		2	0	0
手足皮膚症候群		0	1	0	–		1	0	0
両足関節炎		1	0	0	0		1	0	0

GS療法と因果関係ありの最悪Grade頻度(試験群のみ)

臨床検査値　　42 例(GS療法の症例報告書受領済み)

項目	G1	G2	G3	G4	G1≤	G3-4 (%)	G4 (%)
白血球数減少	9	17	8	3	37	26.2	7.1
好中球数減少	3	12	15	11	41	61.9	26.2
貧血(ヘモグロビン減少)	25	9	1	0	35	2.4	0.0
血小板数減少	21	9	2	2	34	9.5	4.8
AST増加	8	0	0	0	8	0.0	0.0
ALT増加	6	1	0	0	7	0.0	0.0
ALP増加	2	0	1	0	3	2.4	0.0
総ビリルビン増加	0	0	0	0	0	0.0	0.0
クレアチニン増加	0	0	0	0	0	0.0	0.0
低アルブミン血症	6	6	0	0	12	0.0	0.0
低Na血症	0	–	0	0	0	0.0	0.0
高Na血症	5	0	1	0	6	2.4	0.0
低K血症	0	–	0	0	0	0.0	0.0
高K血症	3	0	0	0	3	0.0	0.0

項目	G1	G2	G3	G4	G1≤	G3-4 (%)	G4 (%)
発熱	4	2	0	0	6	0	0
発熱性好中球減少症	0	0	4	0	4	0.10	0
口腔粘膜炎	4	4	3	0	11	0.07	0
下痢	4	0	1	0	5	0.02	0
悪心	9	0	0	–	9	0	–
嘔吐	1	0	0	0	1	0	0
疲労	8	1	1	–	10	0.02	–
食欲不振	9	0	3	0	12	0.07	0
斑状丘疹状皮疹(発疹)	8	5	5	–	18	0.12	–

規定項目以外の有害事象

項目	G1	G2	G3	G4	G1≤	G3-4 (%)	G4 (%)
腸炎	0	0	1	0	1	0.02	0
便秘	1	0	0	0	1	0	0
脱毛症	1	1	–	–	2	–	–
色素沈着	2	0	–	–	2	–	–
手足皮膚症候群	0	1	0	–	1	0	–

手術関連の集計

		試験群	対照群	全体
	割付N=	45	46	91
手術日データあり		40	46	86
手術時間(分)	データ欠測	0	0	0
	平均	442.0	428.9	435.0
	標準偏差	399	391	394.5
	最小値	148	74	74
	最大値	845	1021	1021
術式	データ欠測			
	膵頭十二指腸切除術(PD)	28	24	52
	尾側膵切除術(DP)	9	14	23
	膵全摘出術(TP)	3	2	5
	その他	0	6	6
その他術式:	胆管空腸吻合術、胃空腸吻合術	0	1	1
	胆管空腸吻合術	0	1	1
	胆管空腸吻合術、胆嚢摘出術	0	1	1
	胆嚢摘出術、胆管空腸吻合術、胃空腸吻合術	0	1	1
	試験開腹術	0	1	1
合併切除臓器	あり	15	14	29
	門脈系	14	10	24
	動脈系	0	1	1
	結腸	0	0	0
その他:	門脈系、動脈系	0	1	1
	結腸、胃、十二指腸部分	0	1	1
	左副腎	1	0	1
	脾摘	0	1	1
腹腔洗浄細胞診	データ欠測		2	2
または腹水細胞診	陽性	4	5	9
	陰性	35	38	73
	未実施	1	1	2
手術所見 sT	データ欠測		2	2
(UICC 7th)	sT0	0	0	0
	sT1	2	1	3
	sT2	2	5	7
	sT3	25	27	52
	sT4	11	11	22
	sTX	0	0	0
手術所見 sN	データ欠測		3	3
	sN0	28	25	53
(UICC 7th)	sN1	12	18	30
癌遺残	データ欠測		1	1
	R0	34	33	67
(UICC 7th)	R1	5	4	9
	R2	1	8	9
	RX	0	0	0
病理所見 pT	データ欠測		2	2
	pT0	0	0	0
(UICC 7th)	pT1	1	3	4
	pT2	0	2	2
	pT3	31	26	57
	pT4	7	7	14
	pTX	1	5	6
	pT2,pT3	0	1	1
病理所見 pN	データ欠測		2	2
	pN0	16	6	22
(UICC 7th)	pN1	23	35	58
	pNX	1	3	4

手術関連の集計

続き

		試験群	対照群	全体
	割付N=	45	46	91
病理所見 pM	データ欠測		1	1
	pM0	34	35	69
(UICC 7th)	pM1	6	10	16
pStage	データ欠測		1	1
	IA	1	1	2
(UICC 7th)	IB	0	1	1
	IIA	14	4	18
	IIB	13	22	35
	III	6	7	13
	IV	6	10	16
組織型分類	データ欠測		5	5
(膵癌取扱い規約第6版)	乳頭腺癌	0	2	2
	高分化管状腺癌	13	10	23
	中分化管状腺癌	19	20	39
	低分化腺癌	5	4	9
	腺扁平上皮癌	0	1	1
	粘液癌	0	0	0
	退形成癌	2	0	2
	その他	1	4	5
	IPMC	0	2	2
	IPMC由来浸潤癌(膵頭部、膵尾部とも)	0	1	1
	腺癌	0	1	1
	病理に確認したがIDC以上のことは確定不可	1	0	1
術後退院までの日数	データ欠測	1	0	1
(日)	平均	25.1	28.1	26.7
	標準偏差	21	20	20
	最小値	9	8	8
	最大値	76	104	104
再手術	データ欠測			
	なし	40	44	84
	あり	0	2	2
ありの場合の詳細:	胆管空腸狭窄に対し胆管空腸再吻合	0	1	1
	腹腔ドレナージ術	0	1	1

術後合併症

		試験群	対照群	全体
	N=	45	46	91
手術日データあり		40	46	86
	データ欠測			
術後合併症	なし	22	26	48
	あり	18	20	38
合併症の出現頻度(複数選択あり)				
膵瘻		8	12	20
胃内容排出遅延		3	7	10
出血性合併症		1	0	1
腹腔内膿瘍		2	5	7
創感染		1	1	2
胆汁瘻		0	3	3
胃腸縫合不全・狭窄		1	0	1
肺炎		1	1	2
深部静脈血栓症		0	0	0
心血管障害		0	1	1
脳血管障害		0	0	0

自由記載の事象	試験群	対照群	全体
肝膿瘍	1	0	1
虚血性腸炎	1	0	1
高ビリルビン血症	1	0	1
術中右尿管損傷	1	0	1
創離開	1	0	1
胆管炎	1	0	1
胆管空腸吻合狭窄	0	1	1
腸閉塞	1	0	1
乳び腹水	1	0	1
肺塞栓	0	1	1
発熱	1	0	1
腹水貯留	1	0	1
麻痺性イレウス	0	1	1

PhaseII部分(91例)の非切除率

	試験群	対照群	
登録割付	45	46	
治療開始できず ※	3	0	切除率の分母・分子から除外
下部胆管癌	0	1	
自己免疫性膵炎	0	1	
GS療法開始後～手術前に遠隔転移またはR0/1切除不能な膵腫瘍の増悪	2	–	手術前に増悪して非切除
R2	1	8	
R0/1切除	34	36	

※試験群で治療開始できなかったのは、3例とも術前GS拒否(同意撤回)

	試験群	対照群
非切除率(90%CI)	7.14 (0.63-13.7) %	18.2 (8.65-27.7)%

(参考:第Ⅲ相試験への移行判断規準)

Prep-01試験においては、100例中60例がR0もしくはR1切除が可能であり、非切除割合は40% (90%CI : 31.8～48.7%) であった。このことから本試験においては、非切除率が50%を上回らなければ第Ⅲ相試験へ移行するものとする。すなわち、40例中非切除症例が14例(90%CI:22.6～49.2%)までであれば第Ⅲ相試験へ移行する。ただし、非切除症例が14例を超えた場合でも、対照群の切除率を鑑み、第Ⅲ相試験への移行を判断する。

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ORIGINAL ARTICLE – PANCREATIC TUMORS

Neoadjuvant Chemotherapy with Gemcitabine and S-1 for Resectable and Borderline Pancreatic Ductal Adenocarcinoma: Results from a Prospective Multi-institutional Phase 2 Trial

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ABSTRACT

Background. Surgical resection is the only curative strategy for pancreatic ductal adenocarcinoma (PDAC), but recurrence rates are high even after purported curative resection. First-line treatment with gemcitabine and S-1 (GS) is associated with promising antitumor activity with a high response rate. The aim of this study was to assess the feasibility and efficacy of GS in the neoadjuvant setting.

Methods. In a multi-institutional single-arm phase 2 study, neoadjuvant chemotherapy (NAC) with gemcitabine and S-1, repeated every 21 days, was administered for two cycles (NAC-GS) to patients with resectable and borderline PDAC. The primary end point was the 2-year survival rate. Secondary end points were feasibility, resection rate, pathological effect, recurrence-free survival, and tumor marker status.

Results. Of 36 patients enrolled, 35 were eligible for this clinical trial conducted between 2008 and 2010. The most common toxicity was neutropenia in response to 90 % of the relative dose intensity. Responses to NAC included radiological tumor shrinkage (69 %) and decreases in CA19-9 levels (89 %). R0 resection was performed for 87 % in resection, and the morbidity rate (40 %) was acceptable. The 2-year survival rate of the total cohort was 45.7 %. Patients who underwent resection without metastases after NAC-GS ($n = 27$) had an increased median overall survival (34.7 months) compared with those who did not undergo resection ($P = 0.0017$).

Conclusions. NAC-GS was well tolerated and safe when used in a multi-institutional setting. The R0 resection rate and the 2-year survival rate analysis are encouraging for patients with resectable and borderline PDAC.

Pancreatic ductal adenocarcinoma (PDAC) is associated with poor prognosis and an overall 5-year survival rate of <5 %.[1–3] It is the fourth leading cause of cancer deaths in the United States and Japan.[2,4] A minority of patients present with resectable disease at the time of diagnosis.[4] Surgery is the most effective treatment and the only chance for cure of nonmetastatic PDAC, but recurrence rates are high even after R0 resection.[5,6] The ESPAC-1 trial revealed a significant survival benefit for adjuvant chemotherapy.[7] The CONKO-001 and Japanese trials suggested that adjuvant treatment with gemcitabine offered

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a good chance for prolonged disease-free survival in patients undergoing curative resection of PDAC.[8,9]

Curative resection followed by adjuvant therapy is now the standard treatment for resectable PDAC. However, this strategy is still associated with a 2-year survival of <50 %.[7-10] Neoadjuvant therapy allows for the delivery of chemotherapy and/or radiotherapy to a vascularized primary tumor, provides early treatment of micrometastatic disease, and facilitates the evaluation of biomarkers and surrogate measures of response that can be exploited in the postoperative period.[11] Moreover, a larger proportion of patients may receive an active systemic treatment in the neoadjuvant setting compared with the adjuvant setting, which is associated with surgical complications and delayed recovery after surgery.[12] A population-based study demonstrated improved overall survival in patients with PDAC who underwent neoadjuvant therapy followed by resection compared with a similar cohort who underwent surgery-first resection and adjuvant therapy.[13] Several studies reported that neoadjuvant chemotherapy (NAC) with gemcitabine and platinum agents was safe and associated with a high resection rate and an encouraging survival rate.[14-16] These data suggest that NAC is feasible and effective for patients with resectable PDAC and warrant further investigation.

S-1 (TS-1, Taiho Pharmaceutical) is an oral fluoropyrimidine derivative in which tegafur (the prodrug of 5-fluorouracil, 5-FU), has been combined with two 5-FU-modulating substances: 5-chloro-2,4-dihydroxypyridine and potassium oxonate.[17] S-1 monotherapy is associated with antitumor activity in chemonaive patients or in patients with gemcitabine-refractory metastatic PDAC.[18,19] The combination of S1 and gemcitabine (GS) for the first-line treatment of unresectable PDAC was associated with promising antitumor activity and acceptable toxicity.[20-23] On the basis of encouraging results in patients with unresectable PDAC, Miyagi HBPCOG initiated a multi-institutional phase 2 trial to evaluate the feasibility and efficacy of NAC-GS for PDAC (UMIN-CTR, #000001504).

PATIENTS AND METHODS

Eligibility Criteria and Patient Evaluation

This multi-institutional phase 2 cooperative group study was open to patients with PDAC. Between November 2008 and April 2010, a total of 36 patients from nine participating institutions from northeastern Japan were enrolled onto this trial.

Inclusion criteria were as follows: (1) newly diagnosed PDAC; (2) age ≥ 18 years; (3) Eastern Cooperative Oncology Group performance status of 0–1; (4) complete history and physical examination, and staging evaluation requiring multidetector-row computed tomography (MD-CT); (5) no distant metastases; (6) tumor considered as potentially or borderline resectable; (7) no previous antitumor treatment except for biliary drainage; and (8) adequate hematologic, hepatic, renal, and cardiopulmonary functions. Tumor with encasement of the portomesenteric vein and/or abutment of major arteries (hepatic or mesenteric artery) within 180° was defined as borderline. This study was approved by the institutional review board of Tohoku University and each participating institution. Written informed consent was obtained from all patients before the initiation of therapy.

Treatment Regimen and Dose Intensity

Gemcitabine was provided at a dose of 1,000 mg/m^2 on days 1 and 8 of each cycle. S-1 was administered orally at a dose of 40 mg/m^2 twice daily for the first 14 consecutive days followed by a 7-day rest. Each cycle was repeated every 21 days. Patients received two cycles of this regimen. During the preoperative treatment, patients underwent an interim medical history, physical examination, and laboratory studies. Toxicity of the treatment was evaluated by the Common Toxicity Criteria (CTCAE, version 3.0). After completion of two cycles of GS, surgery was planned to occur at 1–6 weeks, and all patients underwent restaging studies with MD-CT to exclude disease progression and to assess resectability. Relative dose intensity for each individual drug was calculated and defined as the dose intensity achieved relative to the standard schedule of each drug.

Resectability and Surgery

After NAC, patients with disease that demonstrated potentially or borderline resectability without newly detected distant metastases were referred for R0-directed pancreatectomy. After exploration and confirmation of resectability, subtotal-stomach-preserving pancreatoduodenectomy (SSPPD) for neoplasm in the head lesion or distal pancreatectomy (DP) for neoplasm in the body or tail was performed. A subtotal-stomach-preserving total pancreatectomy (SSPTP) was performed for the neoplasm extending from the head to body. When the tumor was not separable from the superior mesenteric artery or aorta, the case was considered to be unresectable. For neoplasm infiltrating the portal vein, en-bloc vascular resection was performed. For neoplasm in the body or tail involving the common hepatic artery, en-bloc celiac axis resection (DP-CAR) was performed.[24]

Assessment of Treatment Responses and Surgical Outcomes

Radiographic responses were determined by a comparison of pretreatment MD-CT and preoperative scans.

Response evaluation criteria in solid tumors (RECIST) were used to assess the type of response.[25,26] Serum tumor marker response was determined by a comparison of pretreatment and preoperative levels of carbohydrate antigen 19-9 (CA19-9) values. In the case of biliary obstruction, pretreatment bilirubin level was recorded as total bilirubin level <3.0 mg/dL after biliary drainage. Level of tumor marker was also measured within 2 months after operation to evaluate for normalization.

Information regarding surgery after the completion of the protocol included the type of operation, duration of the operation, estimated blood loss, complications, and 30-day mortality rate. Designated pathologists at each institution examined resected specimens, and their review included the size of the primary tumor, resection margins, and lymph node status. Tumor grade and stage were reported according to the American Joint Committee on Cancer staging manual.[27] Pathological response by the chemotherapy was evaluated by central review according to the classification reported by Evans et al.[28]

Survival

Patient follow-up was performed by MD-CT every 2 months and serum tumor marker level every month after resection. Patients not undergoing operation or resection were followed at the treating institutions or by their primary physicians.

Statistical Analysis

In this single-arm phase 2 trial, the primary end point was the 2-year survival rate. The study was designed to detect an increase in the 2-year survival rate from 25 % expected NAC to 45 %, with a one-sided alpha of 5 % and a power of 80 %. Secondary end points were the resectability, histological and tumor marker response, and disease-free survival. Both the 2-year survival rate and the disease-free survival were estimated according to the Kaplan–Meier method. Variables were compared by Student's *t* test by JMP software, version 10.0.

RESULTS

Patient Characteristics

Of the 36 patients enrolled, 35 were eligible for participation in this clinical trial. One ineligible patient had distant metastases that were discovered after study enrollment (Fig. 1). Feasibility of NAC was assessed in 35 patients, and patient demographics are shown in Table 1. The treating surgeon determined the initial assessment of resectability, with subsequent confirmation by the central reviewer (FM). Among all eligible cases, 19 patients (54 %) were considered to have resectable disease and 16 patients (46 %) were considered to have borderline disease according to our criteria, which were similar to those of the National Comprehensive Cancer Network guidelines.[29]

Dose Intensity and Toxicity

Of 35 eligible patients, 30 (86 %) received two planned cycles of NAC. Five patients required termination of NAC, including two patients who were limited to 0.5 cycles as a result of grade 3 skin rash and three patients who were limited to 1.5 cycles as a result of gastritis or cholangitis. Dose reduction was required in three patients because of grade 4 neutropenia. Mean relative dose intensity of gemcitabine and S-1 was 92.2 and 96.5 %, respectively.

All eligible patients were assessable for adverse events. NAC-related toxicities are listed in Table 2. Four patients developed grade 3 skin rash, and NAC was terminated early in two of these patients. Other grade 3 nonhematological toxicities included cholangitis and gastritis, which required treatment interruption. The most common

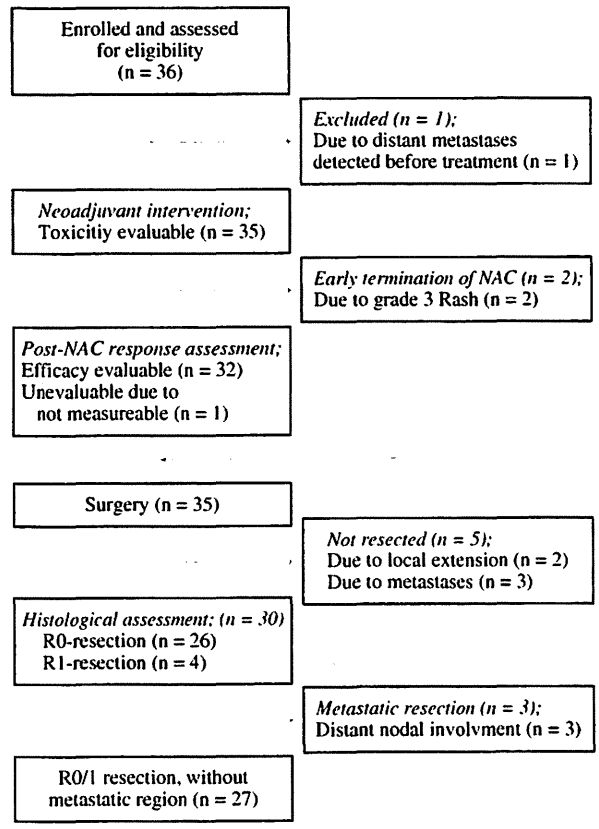

FIG. 1 Flow chart showing the number of patients proceeding through each stage of the study with reasons for exclusion

TABLE 1 Patient demographics

Characteristic	Value
Total cohort eligible	35
Gender (Male:Female)	20;15
Age (years), median (range)	65, 47–77
Location	
Head	25
Body–tail	9
Whole	1
Tumor size (cm), median (range)	2.5, 1.2–7.0
Pretreatment resectability	
Resectable	19
Borderline	16
Pretreatment CA19-9 value (U/ml), median (range)	157.5, <2.0–5,000

nonhematological toxicities were elevations in aminotransferases. In terms of hematological toxicity, neutropenia (63 %) and leukopenia (49 %) were commonly noted. Three patients who experienced grade 4 neutropenia required dose reduction of gemcitabine. One patient developed grade 3 thrombocytopenia. All patients recovered, and there was no treatment-related death in the preoperative period.

Radiologic Tumor Response

Of the 35 patients, 33 had data pairs for baseline and post-NAC follow-up MD-CT available for centralized review. In one patient, tumor size was not measureable as a result of an inability to radiologically identify the border of the tumor. Of the remaining 32 patients with evaluable CT, the estimated median pretreatment size of the tumor was 25 mm, ranging from 12 to 70 mm. Partial response was documented in six patients (19 %) as determined by RECIST of the pre- and post-NAC. The other 26 patients had stable disease. There was no progressive disease documented radiologically. A waterfall plot of the response to characterize antitumor activity demonstrated that 22 patients (69 %) had some degree of tumor shrinkage (Fig. 2a).

Tumor Marker Response

Of 35 patients, 33 had data pairs for baseline and post-NAC serum tumor marker levels. Of 33 patients, 27 patients had levels of CA19-9 above the cutoff (37 U/ml). The median value of CA19-9 for the 27 assessable patients decreased from 274.9 U/ml at baseline to 83 U/ml after NAC ($P < 0.0001$ by Wilcoxon t test). A waterfall plot of the response demonstrated that 24 of 27 patients (89 %) had some degree of CA19-9 decrease and that 15 (56 %) of 27 patients had a more than 50 % decrease in the CA19-9 value (Fig. 2b).

TABLE 2 Treatment-related adverse events ($n = 35$)

Adverse event	Grade[a] 1	2	3	4	1–4, *n* (%)	3/4, *n* (%)
Hematological						
Anemia	7	1	0	0	8 (23)	0
Leukopenia	3	10	4	0	17 (49)	4 (11)
Neutropenia	2	8	9	3	22 (63)	12 (34)
Thrombocytopenia	7	1	1	0	9 (26)	1 (2.9)
Nonhematological						
Fatigue	4	0	0	0	4 (11)	0
Diarrhea	2	0	0	0	2 (5.7)	0
AST elevated	6	4	0	0	10 (29)	0
ALT elevate	5	3	0	0	8 (23)	0
Anorexia	3	0	0	0	3 (8.6)	0
Nausea	3	0	0	0	3 (8.6)	0
Vomiting	1	0	0	0	1 (2.9)	0
Mucositis	4	1	0	0	5 (14)	0
Hyperpigmentation	4	0	0	0	4 (11)	0
Constipation	4	2	0	0	6 (17)	0
Dermatitis	0	1	0	0	1 (2.9)	0
Cholangitis	0	1	2	0	3 (8.6)	2 (5.7)
Rash	3	0	4	0	7 (20)	4 (11)
Gastritis	0	0	2	0	2 (5.7)	2 (5.7)

AST aspartate aminotransferase, *ALT* alanine aminotransferase

[a] Worst grade reported during the preoperative period

Resectability and Surgical Outcomes

According to operative findings, five patients were judged to have unresectable disease due to distant metastases and aggressive local extension (Fig. 1). Thirty (86 %) patients underwent resection with curative intent. Of the operative procedures performed for resection, 19 SSPPD, seven DP, and four SSPTP were performed. Half of operations were standard pancreatectomies with combined resection of adjacent major vessels. Overall perioperative morbidity was 40 % for patients who underwent pancreatectomy. The details of the postoperative complications are listed in Table 3. There was one postoperative death. In this case, there were no abdominal complications, but the patient experienced sudden death from suspected arrhythmia at 2 weeks after surgery. Postoperative gemcitabine was administered in 24 cases (80 %).

Pathological Findings, Including Grade, Stage, and Response to Neoadjuvant Treatment

Histological assessment of resected specimens in 30 cases treated with NAC-GS is summarized in Table 4.

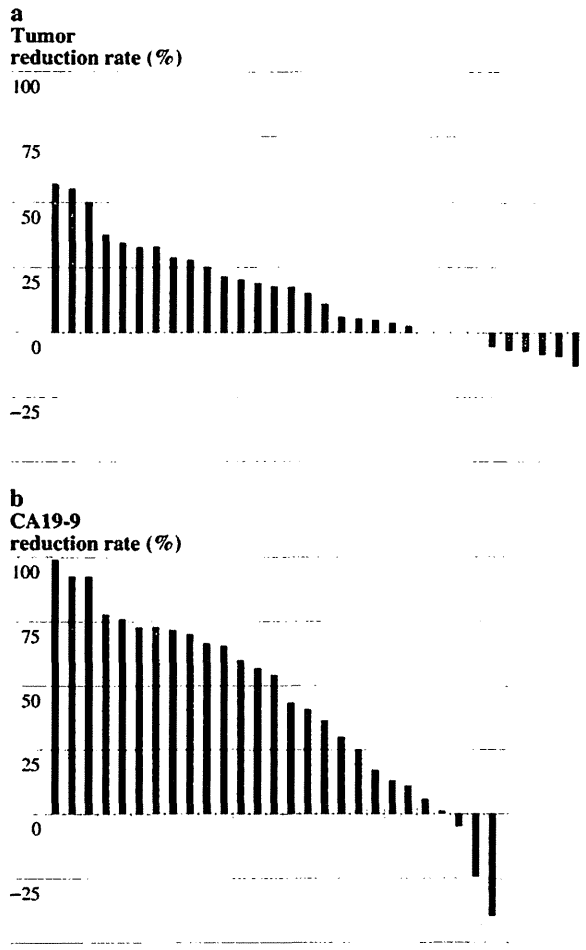

FIG. 2 Waterfall plot of reduction rate for radiological tumor size and serum CA19-9. **a** Radiological tumor reduction rate ($n = 33$). The data represent the rate of tumor size reduction, calculated as [(baseline − posttreatment)/baseline]. There were 5 cases with 0 % reduction. **b** Serum CA19-9 reduction rate ($n = 32$). The data represent the rate of CA19-9 reduction, calculated as [(baseline − posttreatment)/baseline]

The majority of the patients had neoplasm with T3. Nodal involvement was observed in 15 cases (50 %). Three patients had M1 stage IV disease due to the nodal metastases within resected para-aortic lesions. There was no case of macroscopic residual tumor (R2) in resected cases. R0 resection was performed in 26 cases (87 % in resected cases). Histological response evaluation according to Evans' classification revealed six cases that were grade IIB. More than half of the cases were documented as grade IIA.

Survival and Recurrence

The median follow-up time was 19.7 months (95 % confidence interval 17.2–24.6) for all cohorts. The median overall survival was 19.7 months (95 % confidence interval 13.7 to not reached) based on an intent-to-treat analysis. Actuarial 2-year survival rate was 45.7 % (Fig. 3a). Patients who underwent resection without distant metastases ($n = 27$) after NAC-GS had an increased median overall survival (34.7 months) compared with 10.0 months for those without resection or resection with distant metastases ($n = 8$, Fig. 3b). The actuarial 2-year survival rate of the patients with resection was 55.6 %, which was significantly better that the value (12.5 %) in those without resection or with resection including metastases. Median recurrence-free survival for resection without metastases was 20 months. The survival probability at 2-year for initially resectable tumor ($n = 19$) was 57.9 %, which was marginally higher than that for borderline tumors ($n = 16$, 31.5 %) ($P = 0.071$, Fig. 3c).

TABLE 3 Postoperative complications in 30 resections

Complication	Grading by Clavien–Dindo classification[a]	
	Any grade (%)	Grade 3b or more (%)
Pancreatic fistula[b]	3 (10)	0 (0)
Delayed gastric emptying[b]	1 (3.3)	0 (0)
Bile leak	0 (0)	0 (0)
Surgical site infection	2 (6.7)	1 (3.3)
Catheter-related infection	1 (3.3)	0 (0)
Lymph leak	2 (6.7)	0 (0)
Antibiotic-related enterocolitis	1 (3.3)	0 (0)
Cardiovascular complications	1 (3.3)	1 (3.3)
Pulmonary complications	0 (0)	0 (0)
Urinary complications	0 (0)	0 (0)
Total	12 (40)	2 (6.7)

[a] Postoperative complications were listed by grading according to the classification reported by Dindo et al.[37]

[b] Pancreatic fistula and delayed gastric emptying were defined according to the international definition reported by Bassi et al. and Wente et al.[38,39]

DISCUSSION

This study investigated outcomes after NAC-GS for resectable and borderline PDAC. The adverse effects of NAC-GS were similar to those of the same regimen when used for unresectable disease.[30] These adverse effects were manageable, and loss of operative chance due to toxicity was not noted, although there were three cases of early termination of NAC. Compared with other gemcitabine-based regimens, NAC-GS was acceptably safe.[14–16]

One of the potential advantages of NAC is to deliver high dose intensity without the potential delays caused by surgical complications and delayed recovery. The relative

TABLE 4 Pathological findings in 30 resected tumors

Factor	Category	*n* (%)
T	T1	1 (3)
	T2	1 (3)
	T3	28 (93)
N	N0	15 (50)
	N1	15 (50)
M	M0	27 (90)
	M1	3 (10)
Stage	IA	1 (3)
	IB	0 (0)
	IIA	13 (43)
	IIB	13(43)
	III	0 (0)
	IV	3 (10)
Residual tumor	R0	26 (87)
	R1	4 (13)
Treatment effect[a]	I	7 (23)
	IIA	17 (57)
	IIB	6 (20)
	III–IV	0 (0)

[a] Pathological response by the chemotherapy was evaluated by central review according to the classification reported by Evans et al.[28]

dose intensity of NAC-GS was >90 % for both agents. Two-thirds of the patients had documented radiological tumor shrinkage, and most experienced a reduction in tumor markers during NAC. These results indicated that NAC-GS had a modest effect in most patients. A potential drawback of NAC is that delaying surgery may allow disease in some patients to progress to an unresectable stage. In this series, ~10 % of the cases had radiological tumor progression, although none of the progressive changes reached the progressive disease criteria defined by RECIST. All patients, including the patients in whom the tumor progressed but remained resectable or borderline at the time of surgery, had a favorably high resection rate (86 %) and R0 resection rate (74 %, intent to treat based) compared with previous series.[31–33]

The survival impact of neoadjuvant therapy is difficult to estimate or compare with that from other reports. This is primarily the result of the heterogeneity of the patient population in previous studies.[34] The optimal strategy for resectable and borderline PDAC remains controversial. Surgery followed by postresectional systemic chemotherapy with gemcitabine provided a 2-year survival rate of 45–50 %, which was significantly better than that provided by surgery alone.[8–10] Although adjuvant chemotherapy is the optimal therapy for patients with PDAC that is resected without macroscopic residual tumor, all patients who underwent planned resection did not gain a survival benefit. This is because metastatic and/or severe local extension was found after laparotomy in some patients or because these patients experienced delayed recovery from surgical morbidity.[35] Taking these factors into consideration, the 2-year survival obtained with surgery and adjuvant chemotherapy for eligible patients in this study would be estimated as ~30–40 % based on an estimated

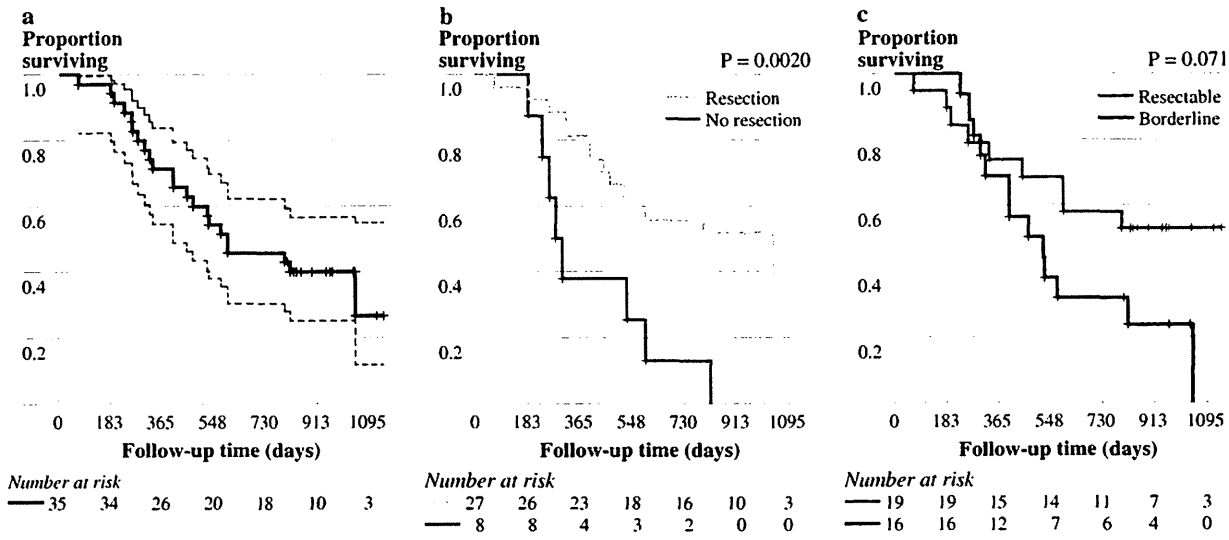

FIG. 3 Kaplan–Meier plots of survival. **a** Overall survival for the entire cohort ($n = 35$). **b** Survival comparison between with and without resection. *Yellow line* indicates resection without distant metastases ($n = 27$). *Green line* indicates patients without resection or resection with distant metastases ($n = 8$). **c** Survival comparison between initially resectable and borderline tumors. *Red line* indicates the initially resectable tumors ($n = 19$). *Purple line* indicates the initially borderline tumors ($n = 16$)

resectability of 70–80 % (compared with 45.7 % of all cohorts in this study). Because no controlled randomized trials have ever compared adjuvant to neoadjuvant therapy, comparison between subgroups could only be performed in a descriptive manner.

A phase 3 study was recently initiated to determine the efficacy of neoadjuvant gemcitabine and platinum for patients with resectable PDAC.[36] GS may also be a good candidate for control studies comparing adjuvant and neoadjuvant therapy. In conclusion, NAC-GS was well tolerated and safe when used in a multi-institutional setting. The R0 resection rate and 2-year survival rate are encouraging for patients with resectable and borderline PDAC.

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