Table 2 Univariate analyses on survival

Factor	*N*	HR	95 % CI	*p* value	*N*	HR	95 % CI	*p* value
Age								
<60	36	1			270	1		
≥60	46	1.13	0.70–1.82	0.630	464	1.16	0.99–1.38	0.074
Sex								
Male	70	1			458	1		
Female	12	1.62	0.82–3.19	0.166	276	1.09	0.93–1.29	0.293
Performance status								
0–1	78	1			681	1		
≥2	4	16.3	4.09–65.2	<0.001	53	3.30	2.44–4.47	<0.001
Disease status								
Inoperable	47	1			506	1		
Recurrent	35	0.77	0.47–1.26	0.300	228	0.73	0.61–0.87	<0.001
Pathology								
Intestinal	39	1			195	1		
Diffuse	43	1.57	0.97–2.54	0.067	521	1.29	1.07–1.56	0.008
Number of metastases								
1	42	1			546	1		
≥2	40	1.42	0.88–2.28	0.153	188	1.47	1.23–1.77	<0.001
Liver metastasis								
Absent	59	1			538	1		
Present	23	1.97	1.19–3.27	0.009	196	1.16	0.97–1.39	0.104
Peritoneal metastasis								
Absent	61	1			332	1		
Present	21	1.22	0.71–2.08	0.467	402	1.00	0.85–1.18	0.991
Lung metastasis								
Absent	61	1			694	1		
Present	21	0.37	0.20–0.68	0.001	40	0.90	0.63–1.29	0.563
Bone metastasis								
Absent	78	1			690	1		
Present	4	2.07	0.49–8.78	0.322	44	1.35	0.97–1.89	0.076
Lymph node metastasis								
Absent	36	1			518	1		
Present	46	1.16	0.71–1.89	0.543	216	1.15	0.97–1.37	0.118
Abdominal lymph node								
Absent	48	1			537	1		
Present	34	0.92	0.57–1.50	0.737	197	1.14	0.95–1.37	0.145
Mediastinal lymph node								
Absent	65	1			712	1		
Present	17	1.29	0.71–2.34	0.400	22	1.28	0.81–2.03	0.286
Cervical lymph node								
Absent	75	1			704	1		
Present	7	2.32	0.98–5.47	0.055	30	1.16	0.77–1.73	0.480

AEGJ adenocarcinoma of esophagogastric junction, *GAC* gastric adenocarcinoma, *N* number of patients, *HR* hazard ratio, *CI* confidence interval

metastasis, and less peritoneal metastasis than patients with gastric cancer are consistent with those of previous reports.

The median survival time of patients with advanced AEGJ was 13.0 months, and there was no significant difference in survival between the patients with AEGJ and those with GAC ($p = 0.445$) in our analysis. In the patients treated with the F + P chemotherapy regimen, the OS was not significantly different between AEGJ and GAC ($p = 0.352$). These survival data for the patients receiving F + P is almost the same as those for inoperable gastric cancer patients who were enrolled and received F + P in Japanese phase III trials [11–13].

Table 3 Multivariate analysis on survival

Factor	Patients with AEGJ			Patients with GAC		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Performance status						
0–1	1			1		
≥2	10.56	2.68–41.86	0.001	3.15	2.32–4.27	<0.001
Disease status						
Inoperable				1		
Recurrent			NE	0.76	0.63–0.91	0.002
Pathology						
Intestinal				1		
Diffuse			NE	1.32	1.09–1.59	0.004
Number of metastases						
1				1		
≥2			NE	1.45	1.21–1.75	<0.001
Liver metastasis						
Absent	1					
Present	2.22	1.31–3.78	0.003			NE
Lung metastasis						
Absent	1					
Present	0.33	0.18–0.63	0.001			NE

AEGJ adenocarcinoma of esophagogastric junction, *GAC* gastric adenocarcinoma, *N* number of patients, *HR* hazard ratio, *CI* confidence interval, *NE* not evaluated

We identified poor PS, the presence of liver metastasis, and absence of lung metastasis as baseline prognostic factors in patients with inoperably advanced or recurrent AEGJ. Several studies have identified prognostic factors for patients with metastatic gastric cancer who received first-line chemotherapy: poor PS, the presence of liver, peritoneal, or bone metastases, microscopically scirrhous type tumors, and number of metastatic sites [25, 26]. Chau et al. [27] also elucidated that poor PS and the presence of liver or peritoneal metastases was associated with poor prognosis for patients with advanced esophageal, EGJ, and gastric cancer. The prognostic factors in AEGJ identified in our report are compatible with the prognostic factors reported in EGJ and gastric cancer.

Chau et al. [8] reported that the survival curves of patients with advanced AEGJ and GAC almost overlapped and so it might not be necessary to distinguish patients with advanced esophagogastric adenocarcinoma according to primary tumor origin. Our results were consistent with this report. We consider that the same chemotherapy can be given to both patients with inoperably advanced or recurrent AEGJ and those with GAC in the clinical practice in Japan, and Japanese future trials on gastric cancer chemotherapy can include both subgroups.

This study had several limitations because it was a retrospective, single-institution study. First, because the selection of chemotherapy regimen in patients with AEGJ was not standardized, the study included several chemotherapy regimens and tumor location itself might have influenced regimen selection, although differences were not statistically significant. Second, disease progression was judged by the investigators in this study.

In conclusion, we identified that the incidence, characteristics, treatment outcomes, and prognosis for patients with AEGJ showed no significant differences compared with those for patients with GAC. We consider that Japanese future trials on gastric cancer chemotherapy can include both subgroups.

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化学療法

一次治療・二次治療のレジメン選択

The choices of regimen in first and second-line of advanced gastric cancer

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Key words：gastric cancer, chemotherapy, choices of regimen, nab-paclitaxel, ramucirumab

はじめに

胃癌の死亡率は，我が国では男性では肺癌に次ぎ2位，女性では3位となっており，切除不能・再発胃癌に対する化学療法の発展が望まれている．

1990年代に，胃癌に対するbest supportive care(BSC)とフッ化ピリミジンを含む化学療法との比較試験において，化学療法群での生存期間の延長が次々と報告され[1-3]，胃癌に対する化学療法の有用性が証明された．この頃より，世界で多くの臨床試験が行われ，現在切除不能・再発胃癌に対する標準的な一次治療はフッ化ピリミジン製剤と白金製剤の併用療法であるとされているが，世界的に統一された標準治療は存在しない．また，胃癌の転移形式や患者の全身状態によって，標準治療を行うことができない場合もあり，薬剤の選択は非常に重要なものとなる．

本稿では，切除不能・再発胃癌を対象とした臨床試験の結果をもとに，我が国における胃癌に対する一次治療および二次治療の選択肢について概説する．

1 一次治療

1) 切除不能・再発胃癌に対する標準的な一次治療

近年の切除不能・再発胃癌に対するエビデンスとして，欧州からはREAL2試験[4]によりECF(epirbicin+oxaliplatin+5-fluorouracil(5-FU))の三剤併用療法が，米国からはV325試験[5]によりDCF(docetaxel+cisplatin(CDDP)+5-FU)の三剤併用療法が標準として位置づけられている．しかしながら，DCF療法についてはその毒性から，高齢者やPS不良例においては必ずしも行われておらず，フッ化ピリミジン製剤と白金製剤の二剤併用療法も行われている．

我が国においては，1990年代にJCOG9205[6]において，5-FU持続静注を標準治療とし，FP療法とUFT(tegafur-uracil)+mitomycin C療法がそれぞれ比較検討されたが，併用療法における生存期間の延長は認められず，安全性からも5-FU持続静注が標準治療と考えられた．これを受け，JCOG9912[7]では5-FU持続静注を標準治療とし，S-1療法とirinotecan(CPT-11)+CDDP療法がそれぞれ比較検討され，S-1療法の5-FU持続静注に対する非劣性が証明された．また，同時期に行われたS-1療法とSP(S-1+CDDP)療法の比較第III相試験であるSPIRITS

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試験[8]では，SP療法は，全生存期間(OS)，無増悪生存期間(PFS)，奏効割合(RR)，いずれにおいても有意に上回ることが報告された．これらを含め，表1に示す臨床試験の結果より，現在我が国における切除不能・再発胃癌に対する一次治療の標準はSP療法であると考えられている．CDDPのdose intensityを更に高める目的で，切除不能・再発胃癌を対象として3週ごとのSP療法と5週ごとのSP療法とを比較検討する第III相試験(SOS試験)[9]が韓国と我が国の共同試験として行われた．PFS中央値は，5週ごと投与群が4.9カ月であったのに対し，3週ごと投与群では5.5カ月と有意に良好であった(HR=0.82，95%CI 0.68-0.99，p=0.0418)．MSTは，3週ごと投与群が14.1カ月，5週ごと投与群が13.9カ月であり，有意差は認められなかった(HR=0.99，95%CI 0.81-1.21，p=0.907)．Grade 3以上の毒性は，5週ごと投与群で好中球減少9%，貧血9%であったのに対し，3週ごと投与群では好中球減少39%，貧血19%と高かった．非血液毒性はほぼ同等であった．3週ごとのSP療法が主要評価項目であるPFSで優越性を示したが，OSで有意差を認めておらず，血液毒性の頻度を考慮すると，5週ごとのSP療法を否定するものではないと考える．

また一方で，CDDPは腎機能障害を認める症例には腎毒性の問題から投与しにくく，またhydrationも必要であり，投与可能な症例がある程度限定される．そこでoxaliplatin(L-OHP)とS-1の併用療法であるSOX療法の開発が行われた．切除不能・再発胃癌を対象として，標準療法であるSP療法に対するSOX療法の非劣性を検証する第III相試験[10]が行われ，PFS中央値はSOX群で5.5カ月，SP群5.4カ月とSP療法に対するSOX療法の非劣性が示された(HR=1.004，95%CI 0.840-1.199)．Grade 3以上の有害事象では，白血球減少，好中球減少，貧血，発熱性好中球減少症がSOX群で有意に低く(p<0.0001)，末梢神経障害はSOX群で有意に高かった(p<0.0001)．OSの結果が待たれるが，今後L-OHPが胃癌に対して保険承認され，選択肢が更に広がることを期待したい．

一方，消化器癌領域においても分子標的薬の開発が急速に行われ，多くの切除不能・再発胃癌に対する第III相試験が行われたが，一次治療において有効性を示すことができたのはtrastuzumabのみである(表2)．これまで胃癌では，HER2陽性胃癌が未分化癌に比べ分化型腺癌で多いことが報告されていたが，その後の観察研究(JFMC44-1101)[11]においても，分化型腺癌，Lauren分類における腸管型，肝転移が特にHER2陽性との相関が高いとの報告がなされている．日本人におけるHER2陽性割合は21.1%で，後述するToGA試験でのHER2陽性割合の22.1%と同等であったが，本試験では選択バイアスが否定できず，実際にはACTS-GC試験[12]で報告された13.6%前後と思われる．ToGA試験においては，免疫染色(IHC)3+またはFISH(fluorescence *in situ* hybridization)陽性で定義したHER2の過剰発現を認める切除不能・再発胃癌，胃食道接合部癌を対象として，XP/FP療法への抗HER2抗体であるtrastuzumabの上乗せ効果が，OS，PFS，RRいずれにおいても証明された．我が国から登録された症例は全例XP療法をbaseとして行われていたこともあり，HER2陽性胃癌に対してはXP療法にtrastuzumabを併用することが推奨される．更に，HER2陽性切除不能・再発胃癌を対象として，SP療法(3週ごと投与)にtrastuzumabを併用する第II相試験(HERBIS-1)が行われ，RR 67.9%と高い奏効が報告されている．現在，HER2陽性切除不能・再発胃癌に対するSP療法(5週ごと投与)とtrastuzumabの併用療法の第II相試験(T-SPACE)がWJOG(西日本がん研究機構)において進行中である(UMIN000008389)．

2) 高度の腹膜播種を伴う切除不能・再発胃癌に対する治療

腹膜転移症例においては，腹水貯留，腸閉塞，尿管閉塞や総胆管閉塞などの合併症をきたすことが多く，そのため標準的な化学療法を行うことが難しい症例も少なくない．腸閉塞もしくは大量腹水により経口摂取が困難な場合には，経口抗癌薬であるS-1やcapecitabineは内服・吸収が不安定となり，また，大量腹水を認める症

表1　我が国における切除不能・再発胃癌に対する一次治療の主な第III相試験

試験名	相	レジメン	患者数	奏効割合(%)	無増悪生存期間(月)	全生存期間(月)
JCOG9912	III	5-FU continous infusion	234	9	2.9	10.8
		CPT-11+CDDP	236	38	4.8(p<0.001)	12.3
						HR=0.85, 95%CI 0.70-1.04, p=0.05
		S-1	234	28	4.2(p=0.001)	11.4
						HR=0.83, 95%CI 0.68-1.01, p=0.025
SPIRITS	III	S-1+CDDP(SP)	148	54	6.0	13.0
		S-1	150	31	4.0	11.0
					p<0.0001	HR=0.77, 95%CI 0.61-0.98
						p=0.04
TOP-002	III				median TTF	12.8
		S-1+CPT-11(IRI-S)	155	26.9	4.5	10.5
		S-1	160	41.5	3.6	HR=0.856, 95%CI 0.663-1.106
					p=0.157	p=0.2327
ISO-5FU10	III	S-1	88	29.5	4.0	10.3
		5-FU/l-LV(RPMI)	89	23.6	3.5	8.3
					HR=0.76, 95%CI 0.55-1.06	HR=0.84, 95%CI 0.60-1.18
						non-inferiority
START	III	S-1+docetaxel	310	30.3	161 days	390 days
		S-1	313	18.4	126 days	334 days
					HR=0.74	HR=0.88, 95%CI 0.735-1.044
					p=0.0004	p=0.1416
ASCO-GI 2013 abstr#60 K.Higuchi et al.	III	S-1+L-OHP(SOX)	340	55.7	5.5	not reported
		S-1+CDDT(SP)	340	82.2	5.4	
					HR=1.004, 95%CI 0.840-1.199	
					non-inferiority	

表2　胃癌における分子標的薬の主な第III相試験

	試験名	相	治療ライン	レジメン	患者数	奏効割合(%)	無増悪生存期間(月)	全生存期間(月)
EGFR	ToGA	III	1st	FP/XP+trastuzumab (IHC 3+ or FISH+)	584	47.3 p=0.0017	6.7 HR=0.71, p=0.0002	13.8 HR=0.71, p=0.0046
				FP/XP+trastuzumab (IHC 2+/3+ or FISH+)				16 HR=0.65
	EXPAND	III	1st	XP±cetuximab	904	29	4.4 HR=1.091 p=0.3158	9.4 HR=1.004 p=0.9547
	REAL-3	III	1st	EOC±panitumumab	200	46 p=0.467	7.4 HR=1.22 p=0.068	8.8 HR=1.37 p=0.013
	LoGIC	III	1st	XELOX±lapatinib	545	53 40	6.0 HR=0.82 p=0.0381	12.2 HR=0.91 p=0.3492
	TyTAN	III	2nd	paclitaxel±lapatinib	132 129	27 9	5.4 HR=0.85 p=0.2441	11.0 HR=0.84 p=0.2088
VEGF	AVAGAST	III	1st	XP±bevacizumab	387 387	46 p=0.0315	6.7 HR=0.80 0.0037	12.1 HR=0.87 p=0.1002
	REGARD	III	2nd～	ramucirumab+BSC placebo+BSC	238 117	3.4 p=0.756	2.1 HR=0.483 p=0.0001	5.2 HR=0.776 p=0.0473
others	GRANITE-1	III	2nd-3rd	everolimus placebo	656	4.5	1.68 HR=0.66 p<0.0001	5.39 HR=0.90 p=0.1244

例においては，hydrationにより腹水の増悪をみることが多いためCDDPの投与が難しく，標準療法であるSP療法やXP療法を行うことができない．前述してきた臨床試験(JCOG9912試験，SPIRITS試験，ToGA試験)や，その他の多くの試験においても高度の腹膜播種症例は対象からは除外されており，標準治療は確立されていない．

JCOG0106試験[13]では，画像上消化管狭窄もしくは腹水を指摘できる腹膜転移症例を対象として，5-FU持続静注とMF(methotrexate+5-FU)療法が比較された．5-FU持続静注に対してMF療法は生存期間中央値(MST: median survival time)で9.4カ月に対し，10.6カ月と優越性を示すことができなかった(HR=0.94，95%CI 0.72-1.22，p=0.31)．本試験でも，高度の腹膜転移症例は除外されていたが，5-FU持続静注は安全性も十分許容される結果であったことから，そのような症例に適応可能と考えられる．

一方，経口摂取可能な切除不能・再発胃癌を対象として，5-FU/l-LV療法のS-1療法に対する非劣性がISO-5FU10試験[14]で証明されているため，経口摂取が困難な腹膜転移症例には，5-FU/l-LV療法も選択肢の一つとして考えられる．

前述のCDDPやS-1のほか，腹膜転移症例では，下痢や便通のコントロールが困難であり，CPT-11の投与も難しい．よって，タキサン系薬剤が選択肢の一つとなりうる．高度腹水または経口摂取不能の腹膜転移を有する胃癌を対象として，両剤を併用したFLTAX療法の安全性確認試験が行われ，第II相部分では，腹水に対する効果は47%，PFS中央値は6.2カ月，MST 9.5カ月と良好な成績が報告されている[15]．これを受け，高度腹水または経口摂取不能の腹膜転移を有する胃癌を対象として，5-FU/LV療法とFLTAX療法の無作為化比較第II/III相試験(JCOG1108/WJOG7312G)が現在進行中であり，結果が待たれる．

3) 高齢者の切除不能・再発胃癌に対する一次治療

高齢者の胃癌患者は増加しており，今後ますます高齢者におけるレジメンの選択は重要になってくるであろう．高齢者は，骨髄・肺・肝臓・腎臓などの主要臓器能が低下している傾向にあり，また栄養状態やPS(performance status)が低下している患者も多く，若年者の胃癌患者に対する化学療法と同様の標準治療を行えない場合が多い．SPIRITS試験のsubgroup解析においては，60歳未満に比べ，60歳以上の患者では，S-1療法に対するSP療法の生存期間への上乗せは小さい傾向にあった(HR=0.75，95% CI 0.61-0.92)．高齢者に対するSP療法については，国内外で後ろ向きの検討も幾つか報告されているが，結果は一定でない．S-1療法に関しては，韓国において65歳以上の切除不能・再発胃癌患者を対象として，capecitabineとS-1が比較されたselection designの無作為化第II相試験[16]において，capecitabine群，S-1群ではPFS中央値がそれぞれ4.7カ月，4.2カ月(HR=1.0，95%CI 0.61-1.63)，MSTは9.5カ月，8.2カ月(HR=0.98，95%CI 0.62-1.55)と両群に有意差は認めず，S-1群でも比較的良好な結果が報告されている．Grade 3/4の好中球減少はS-1群で4.8%，倦怠感7.1%，食欲不振は9.5%，capecitabine群で6.8%，9.1%，6.8%と，毒性についてもcapecitabineと比較しても許容できるものであった．

現時点では，臨床的に適切な高齢者の定義自体もいまだ定まっておらず，標準治療を決定することはできないが，臓器機能やPSなどの全身状態を十分に考慮に入れ，SP療法やS-1療法を検討しているのが現状である．

2 二次治療

1990年代にCPT-11，paclitaxel，docetaxelなどの薬剤が開発されて以来，我が国においては，二次治療としての明らかな有効性が示されないまま，切除不能・再発胃癌に対してこれらの薬剤による二次治療が行われていた．

切除不能・再発胃癌に対する二次治療として，CPT-11とBSCとを比較する第III相試験[17]がドイツで行われたが，登録スピードが遅く途中中止となり，結論が得られていなかった．しかし，CPT-11群で生存期間の延長が認められており，二次治療の有効性を示唆していた．これに続き韓国で行われた，CPT-11もしくはdocetaxelを行う化学療法群とBSC群とを比較した第III相試験[18]で，化学療法群でOSの有意な延長が報告され，切除不能・再発胃癌に対する二次治療の有効性が初めて示された．イギリスでも，docetaxel群と積極的な症状管理（ASC: active symptom control）群が第III相試験（COUGAR-02）[19]で比較され，docetaxel群でMSTが5.2カ月，ASC群のMSTが3.6カ月（HR=0.67，95% CI 0.49-0.92，p=0.01）とOSの有意な延長が報告された．アジアだけでなく，欧州においても二次治療の有効性が示されたこととなる．

一方，我が国では，BSCとの比較ではなく，フッ化ピリミジン製剤と白金製剤による一次治療に不応となった切除不能進行胃癌を対象として，weekly paclitaxel（wPTX）療法とCPT-11療法を比較した第III相試験（WJOG4007）[20]が行われた．MSTはwPTX群で9.5カ月，CPT-11群では8.4カ月であり，PTXに対するCPT-11の優越性は示されなかった（HR=1.13，95% CI 0.86-1.49，p=0.38）．また，PFS中央値は，wPTX群，CPT-11群でそれぞれ3.6カ月，2.3カ月（HR=1.14，95%CI 0.88-1.49，p=0.33）であった．三次療法への移行割合はCPT-11群の71％に対して，wPTX群では89％と有意に高かった（p=0.04）．この試験結果からは，フッ化ピリミジン製剤と白金製剤の併用療法に不応となった切除不能・再発胃癌に対する二次治療としては，タキサン系薬剤が忍容性，治療効果ともに期待できるレジメンではあるが，CPT-11療法もまた世界的に広く行われている治療法であり，その有効性は否定されるものではないと考える．

また，フッ化ピリミジン製剤を含む一次治療に不応となった胃癌腹膜転移症例を対象として，best available 5-FU療法（初回化学療法の内容により，5-FU持続静注もしくはMF療法を選択）とwPTX療法とを比較したselection designの無作為化第II相試験であるJCOG0407試験[21]では，MSTでは両群ともに7.7カ月であり（HR=0.877，95%CI 0.571-1.377，p=0.298），PFSはwPTX群で3.7カ月と有意に良好であった（HR=0.568，95%CI 0.369-0.873，p=0.004）．wPTX療法はフッ化ピリミジン製剤不応の腹膜転移症例の二次治療として有効性を示し，その後の第III相試験における治療の候補であることが示された．しかし，この試験においては，wPTXによるOSの延長は示されておらず，クロスオーバーが67％の症例に認められたことがその要因と考えられた．

また，切除不能・進行胃癌患者の二次治療におけるnab-paclitaxelの有効性を検証した第II相試験（J-0200試験）で，PFS中央値2.9カ月，MST 9.2カ月との結果を受け，2013年2月にnab-paclitaxelが胃癌に対し，保険承認された．現在，フッ化ピリミジン製剤に不応となった症例を対象に，paclitaxelとの比較第III相試験が進行中であり，結果が待たれる．

我が国で行われたTCOG GI-0801試験[22]では，S-1を含む化学療法に不応の切除不能・再発胃癌を対象として，biweekly CPT-11+CDDP療法とCPT-11療法が比較され，PFS中央値はそれぞれ3.8カ月，2.8カ月（HR=0.68，95%CI 0.47-0.98，p=0.0398），MSTはそれぞれ10.7カ月，10.1カ月（HR=0.98，95%CI 0.69-0.144，p=0.982）であった．CP群で主要評価項目であるPFSが有意に延長することが報告された．更に，S-1療法不応の切除不能・再発胃癌を対象として，biweekly CPT-11+CDDP療法とCPT-11がTRICS試験[23]において比較され，PFS中央値はそれぞれ4.63カ月，4.13カ月（HR=0.86，95%CI 0.614-1.201，p=0.372）と有意差は認められなかった．主要評価項目であるOSの解析結果が待たれるが，現時点では，術後補助化学療法としてS-1療法を行っている経過中の再発症例，もしくはS-1療法後6カ月以内の再発症例など，何等かの理由で一次療法でCDDPが投与されていない症例に対する二次治療として，

biweekly CPT-11+CDDP療法は選択肢の一つとなりうると考えられる.

二次治療においても切除不能・再発胃癌に対して多くの分子標的薬が開発されてきたが, 唯一VEGFR-2抗体であるramucirumabが有効性が証明されている薬剤である. フッ化ピリミジン製剤と白金製剤に不応となった転移性胃癌・胃食道接合部癌を対象として, ramucirumabとBSCとを比較する第III相試験(REGARD試験)[24]が行われた. MSTはramucirumab群で5.2カ月, BSC群で3.8カ月(HR=0.776, 95%CI 0.603-0.98, p=0.0473)と, ramucirumab群でOSは有意に延長した. 我が国においては, 標準療法として行っているwPTX療法へのramucirumabの上乗せ効果を検討するRAINBOW試験(ClinicalTrials. gov Identifier: NCT01170663)の結果が待たれるところである.

三次治療については明確なエビデンスはなく, 二次治療に用いなかった薬剤を, 患者の全身状態に合わせて投与しているのが現状である.

おわりに

nab-paclitaxelが胃癌に対して適応を拡大し, oxaliplatinの保険承認が期待されるなど, 切除不能・再発胃癌に対する化学療法の選択肢は更に広がると思われる. また, 一次治療においては, XP/FP+trastuzumab療法へのpertuzumabの上乗せ効果を検討するJACOB試験(ClinicalTrials. gov Identifier: NCT01774786), ECF/XP療法へのMET阻害剤であるrilotumumabの上乗せ効果を検討するRILOMET-1試験(ClinicalTrials. gov Identifier: NCT01697072)などが進行中である. 二次治療においては, trastuzumabに不応となったHER2陽性胃癌に対するTDM-1とpaclitaxel療法を比較するGATSBY試験(ClinicalTrials. gov Identifier: NCT01641939)が進行中であり, また前述のRAINBOW試験は患者登録が終了している. より多くの選択肢が広がり, 長期生存が得られるようになることを期待したい.

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FULL PAPER

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Randomised phase II study of S-1/cisplatin plus TSU-68 *vs* S-1/cisplatin in patients with advanced gastric cancer

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Background: This study aimed to determine whether combination S-1 plus cisplatin (CDDP) therapy, the most widely used therapy for Japanese patients with advanced gastric cancer, and the novel oral antiangiogenic agent TSU-68 could contribute to gastric cancer treatment.

Methods: Ninety-three patients with chemotherapy-naïve unresectable or recurrent advanced gastric cancers were randomised into two groups: TSU-68 plus S-1/CDDP (group A) and S-1/CDDP (group B) groups. Both patient groups received identical S-1 and CDDP dosages. TSU-68 was orally administered for 35 consecutive days. Group B patients received S-1 orally twice daily for three consecutive weeks, followed by intravenous CDDP on day 8. The primary endpoint was progression-free survival (PFS).

Results: Median PFS periods were 208 and 213 days in groups A and B, respectively ($P=0.427$). Median survival periods for groups A and B were 497.0 and 463.5 days, respectively ($P=0.219$). No statistically significant differences were noted for PFS, survival or the adverse event (AE) incidence rate. All AEs were expected according to previous reports for TSU-68, TS-1, and CDDP.

Conclusion: Combination therapy involving TSU-68, S-1, and CDDP was safe and well tolerated in patients with chemotherapy-naïve unresectable or recurrent advanced gastric cancers. However, factors related to therapeutic efficacy should be investigated further.

Gastric cancer is the second most common cause of cancer death both worldwide (Jemal *et al*, 2011) and in Japan (Sobue *et al*, 2012).

Since Macdonald *et al* (1980) reported the use of 5-fluorouracil (5-FU), doxorubicin, and mitomycin-C combination chemotherapy (median survival time, 5.5 months) for the treatment of

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unresectable, advanced, or recurrent gastric cancers in 1980, multidrug chemotherapies, particularly those that include 5-FU, have been the most widely used therapies worldwide. Currently, the employed regimens differ among geographic regions. For example, epirubicin, cisplatin (CDDP), and 5-FU; epirubicin, oxaliplatin, and capecitabine (EOX); and docetaxel, CDDP, and 5-FU chemotherapies are primarily used in the control arms of clinical studies in Western countries, whereas 5-FU and CDDP chemotherapy is primarily used in non-Western countries. Thus, no global consensus has been reached on a standard therapy.

In Japan, the clinical development of chemotherapies for unresectable, advanced, or recurrent gastric cancers has progressed for many years, and many clinical studies have been conducted using TS-1 (S-1), a fluoropyrimidine anticancer drug that is produced in Japan. When compared with continuous intravenous 5-FU infusion, 5-FU/CDDP did not significantly increase life expectancy (Ohtsu *et al*, 2003); since then, 5-FU alone has been used as a reference arm. Nevertheless, the American Society of Clinical Oncology reported the results from two Japanese phase III clinical studies (Japan Clinical Oncology Group (JCOG) 9912 (Boku *et al*, 2009) and S-1 Plus cisplatin *vs* S-1 in RCT in the Treatment for Stomach cancer (SPIRITS) (Koizumi *et al*, 2008)) in 2007. Japan Clinical Oncology Group 9912 demonstrated that S-1 capsule monotherapy was not inferior to continuous intravenous 5-FU infusion in terms of overall survival (OS). In addition, the SPIRITS trial reported a significantly prolonged OS with S-1/CDDP therapy and a better (prolonged by >1 year) OS than that with S-1 alone. Therefore, a first-line standard chemotherapy was established in Japan.

The median survival period achieved in the SPIRITS trial was 13.0 months; therefore, further improvements to the therapeutic results are necessary. In recent years, the use of a fluoropyrimidine anticancer drug in combination with molecular targeted agents has been studied, and vascular endothelial growth factor (VEGF) is assumed to be closely related to tumour proliferation in gastric cancers (Laird *et al*, 2000). The use of bevacizumab, a monoclonal antibody that targets VEGF A, was evaluated in combination with capecitabine and cisplatin as a first-line therapy for advanced gastric cancer (Ohtsu *et al*, 2011). In that study, the progression-free survival (PFS) and overall response rates (ORRs) were significantly improved with bevacizumab; however, no survival benefit related to this drug was noted. On the other hand, ramucirumab, a monoclonal antibody that targets VEGF receptor 2, significantly prolonged OS when used as a second-line monotherapy for advanced gastric or gastroesophageal junction adenocarcinoma (Fuchs *et al*, 2013).

TSU-68 (orantinib) is a novel oral antiangiogenic agent that has been shown to inhibit the tyrosine phosphorylation of VEGF receptor 2, platelet-derived growth factor (PDGF) receptor 6, and fibroblast growth factor (FGF) receptor 1 *in vitro* (Kim *et al*, 2009). Previously, phase I and phase II studies in patients with breast cancer, hepatocellular carcinoma (HCC), lung cancer, and colorectal cancer were conducted in Asia (Kanai *et al*, 2010; Okamoto *et al*, 2012; Shin *et al*, 2012; Toi *et al*, 2012; Inaba *et al*, 2013), and a phase III study was initiated in 2010 to evaluate the survival benefit of TSU-68 in patients with intermediate-stage HCC (ClinicalTrials.gov Identifier: NCT01465464). As part of the clinical development of TSU-68, a combination of S-1/CDDP therapy, the most widely used therapy in Japan for patients with advanced gastric cancers, and TSU-68, which has antiangiogenic effects, was expected to be an effective gastric cancer treatment. Consequently, we conducted a phase II randomised study to compare the effects of a combination therapy with 3 agents—TSU-68, S-1, and CDDP—with the effects of S-1/CDDP therapy with regard to the PFS to improve the therapeutic results of first-line standard chemotherapies.

MATERIALS AND METHODS

Patients. The patients included in the study were $\geqslant 20$ years with (1) histologically or cytologically confirmed adenocarcinoma, (2) unresectable or recurrent gastric cancer, and (3) no prior systemic treatment. Recurrent patients were eligible if the last dose of postoperative adjuvant chemotherapy had been received at least 180 days before the start of the study. Other eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0–1 and adequate functioning of the major organs, along with the following laboratory values: haemoglobin, $\geqslant 8.0\,g\,dl^{-1}$, neutrophil count, $\geqslant 1500\,mm^{-3}$, platelet count, $\geqslant 100\,000\,mm^{-3}$, serum creatinine, $\leqslant$ the reference value at the study center, and serum bilirubin (TBIL), $\leqslant 1.5\,mg\,dl^{-1}$. Other laboratory criteria included a creatinine clearance of $\geqslant 60\,ml\,min^{-1}$, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of $\leqslant 100\,U\,l^{-1}$, and an alkaline phosphatase (ALP) level that was 2.5-fold less than the reference value at the study center. For patients with liver metastases, those with AST, ALT, and ALP values that were 5-fold less than the reference values at the study center were eligible. In addition, patients were required to have target tumours that were measurable by computed tomography, magnetic resonance imaging, or radiography in accordance with the Response Evaluation Criteria in Solid Tumours (RECIST), ver. 1.0. All patients were required to provide written consent. This study was implemented in accordance with Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

Design. This was a phase II, multicenter, randomised, controlled study to estimate the efficacy of TSU-68 plus S-1/CDDP therapy *vs* S-1/CDDP therapy. Randomisation was performed according to the minimisation method, using 'unresectable gastric cancer', 'recurrent gastric cancer with postoperative adjuvant chemotherapy', and 'recurrent gastric cancer without postoperative adjuvant chemotherapy' as the stratification factors. Eligible patients were randomly assigned to either the TSU-68 plus S-1/CDDP (group A) or the S-1/CDDP (group B) groups at a ratio of 1 : 1 (Figure 1).

In groups A and B, S-1 was administered at a dose of $<40\,mg\,m^{-2}$. The S-1 dose was calculated according to the patient's body surface area as follows: $<1.25\,m^2$, 40 mg; 1.25–1.5 m^2, 50 mg; and $>1.5\,m^2$, 60 mg. S-1 was orally administered twice daily for three consecutive weeks. CDDP was administered at a dose of $60\,mg\,m^{-2}$ by intravenous infusion on day 8. The duration of each cycle was 5 weeks (35 days). In group A, 400 mg of TSU-68 was orally administered twice daily (total daily dosage, 800 mg) for five consecutive weeks. The treatments were continued until 1 of the following occurred: progressive disease (PD), unacceptable toxicity, withdrawal of patient consent (regardless of toxicity), or termination of treatment at the discretion of the attending physician.

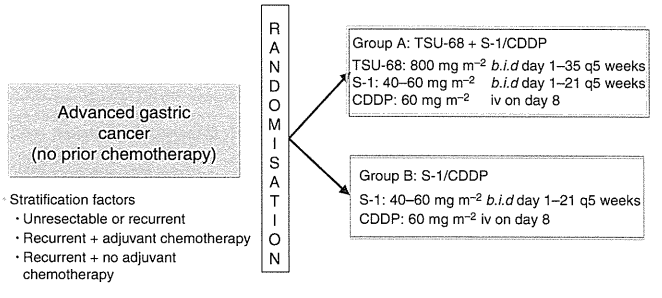

Figure 1. Study design. Two patients were excluded from the full analysis set by an independent data monitoring committee.

The protocol was approved by the Institutional Review Board of each study center. The Independent Data Review Committee evaluated safety throughout the study period. This study was conducted in compliance with the Declaration of Helsinki and the Japanese GCP Guidelines.

Endpoints and evaluation methods. The primary endpoint was PFS, which was defined as the period from the day of enrolment to the day on which (1) radiological or clinical progression was evident, (2) subsequent treatment was indicated, or (3) the patient died. The earliest day among these defined days was considered. If patients were lost to follow-up because of second-line treatment or a transfer to another hospital, their data were censored. Tumours were measured every 5 weeks until the onset of PD. All measured images were assessed by a Central Imaging Review Committee in accordance with the RECIST (New Guideline 2000; Therasse *et al*, 2000).

Secondary endpoints were the antitumour effect (ORR), OS, safety, pharmacokinetics (PK), and the relationship between angiogenesis-related factors and efficacy. To determine safety, blood tests, biochemical analyses, and urinalyses were performed and subjective as well as objective findings were followed-up throughout the study period. Adverse events (AEs) were graded in accordance with the National Cancer Institute Common Toxicity Criteria ver. 3.0.

In the patients who were included in the PK evaluation on day 8, the PK of TSU-68 after repeated administration of TSU-68 (400 mg per dose) on day 8, the PK of tegafur (FT), 5-FU, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo) after the repeated administration of S-1 (50–60 mg per dose), and the PK of the total and free platinum levels after the administration of CDDP (60 mg m^{-2}) were investigated.

Angiogenesis-related factors were tested at baseline levels and before the start of the next cycle. The following angiogenesis-related factors were measured: PDGF-AA, PDGF-BB, soluble vascular cell adhesion molecule-1, soluble endothelial-leukocyte adhesion molecule-1 in the serum and plasma, and interleukin-8 with enzyme-linked immunosorbent assays (ELISAs; BioSource Europe, Nivelles, Belgium); plasma tissue plasminogen activator (t-PA) with a soluble t-PA ELISA kit (Oncogene Science, Cambridge, MA, USA); and plasma plasminogen activator inhibitor-1, acidic FGF, VEGF, VEGF soluble receptor type 2, hepatocyte growth factor, VEGF-C, VEGF soluble receptor type 3, and the lactate dehydrogenase isozyme.

Statistical analyses. The SPIRITS trial that was conducted in Japan showed that the median PFS achieved with S-1/CDDP was 6 months. According to this result, the PFS with TSU-68 + S-1/CDDP was estimated to be 9 months. This would have a significant clinical impact on systemic therapy for advanced gastric cancer. We assumed that a total of 86 patients (two groups) would be necessary to demonstrate the superiority of TSU-68 + S-1/CDDP at a power of 80% and a one-sided significance level of 20% with unstratified log-rank tests at the end of the follow-up period (Rubenstein *et al*, 2005). After considering possibilities such as ineligible patients, we determined that 92 patients were required for the study.

We used a full analysis set (FAS), defined as patients who met the eligibility criteria, for the primary analyses of efficacy and safety.

To compare the PK parameters of S-1 and CDDP between groups A and B, the Wilcoxon test was performed for the maximum drug concentration time (t_{max}), and the Student's *t*-test or Aspin–Welch test was performed for parameters other than the t_{max} after logarithmic transformation.

RESULTS

Patient background. Between December 2008 and February 2012, a total of 93 patients (group A, $n=46$; group B, $n=47$) from a total of 14 centres in Japan were enroled and randomised in this study (Figure 2). One patient from group A was found to be ineligible, and 1 patient from group B did not receive treatment. Therefore, a total of 91 patients (group A, $n=45$ and group B, $n=46$) were included in the FAS that was used for efficacy and safety analyses. There were no significant imbalances in the patient background characteristics at enrolment between the two groups (Table 1). The percentages of patients with 1, 2, or $\geqslant 3$ organs with infiltration and/or metastasis were 46.7%, 40%, and 13.3%, respectively, in group A and 41.3%, 50%, and 8.7%, respectively, in group B. None of the patients had locally advanced disease alone. Peritoneal metastases were noted in 15 (33.3%) group A patients and 15 (32.6%) group B patients. Histologically, diffuse-type and intestinal-type adenocarcinomas were noted in 23 (48.9%) and 22 (51.1%) group A patients, respectively, and in 20 (54.3%) and 25 (43.5%) group B patients, respectively. Gastrectomies had been performed in 6 (19.6%) group A patients and in 9 (13.3%) group B patients before enrolment. Postoperative adjuvant chemotherapy was administered to 4 (10.9%) group A patients and 5 (8.9%) group B patients.

Efficacy

Progression-free survival. The median PFS were not significantly different between the two groups (group A, 208.0 days; group B, 213 days; $P=0.424$; Figure 3).

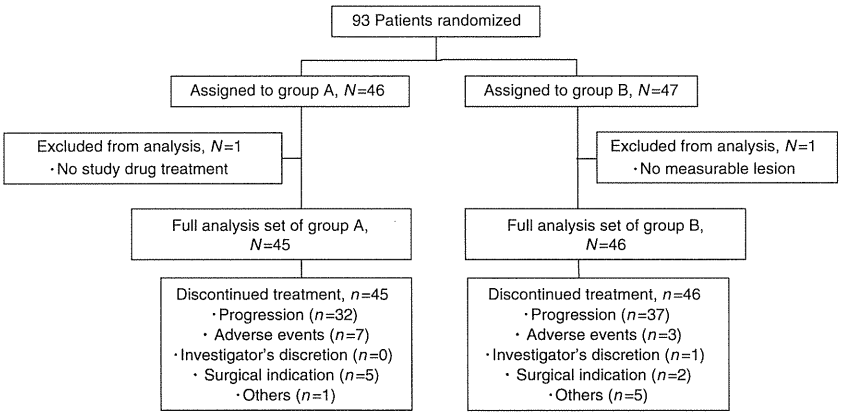

Figure 2. CONSORT diagram. A total of 93 patients (group A, $n=46$; group B, $n=47$) were randomised. One patient from group A did not receive treatment, and 1 patient from group B was ineligible. Therefore, a total of 91 patients (group A, $n=45$; group B, $n=46$) were included in the FAS used for the efficacy and safety analyses.

Table 1. Patient characteristics

Characteristics	No. of patients Group A	Group B	*P*-value
Full analysis set	45	46	
Gender			0.360
Male	30	35	
Female	15	11	
Age, years			0.239
65⩽	26	26	
65>	19	20	
Median (range)	62.0 (30–74)	63.5 (44–76)	
ECOG PS			0.771
0	28	30	
1	17	16	
2	0	0	
Diagnosis			1.000
Unresectable	39	39	
Recurrent	6	7	
Adjuvant chemotherapy			1.000
−	41	41	
+	4	5	
Histology			0.601
Intestinal	22	25	
Diffuse	23	20	
Unknown	0	1	
No. of organs involved			0.847
1	21	19	
2	18	23	
>3	6	4	
Metastasis of peritoneum			1.000
−	30	31	
+	15	15	
Metastasis of liver			0.403
−	26	22	
+	19	24	

Abbreviation: ECOG PS = Eastern Cooperative Oncology Group performance status.

The hazard ratio (HR) was 1.23 (95% confidence interval (CI): 0.74–2.05).

Survival. All follow-up investigations were completed at the time of data cutoff in April 2012, which was 1 year and 8 months after the last patient enrolment. Outcomes were confirmed in all patients (100%). Of the 91 patients in the FAS, 33 of the 45 (73.3%) group A patients and 38 of the 46 (82.6%) group B patients died. The median OS periods were 497.0 days in group A and 463.5 days in group B. The 1-year survival rates were 66.7% in group A and 63.0% in group B. The 2-year survival rate was 30.4% in group A and 22.4% in group B. The survival rates in group A were not significantly different from those in group B ($P = 0.213$) (Figure 3).

The HR was 0.74 (95% CI: 0.46–1.19).

Best overall response. Twenty-eight of the 45 group A patients achieved a partial response (PR), and thus the response rate was 62.2% (95% CI: 46.5–76.2%). Twenty-six of the 46 group B patients achieved a PR, and thus the response rate was 56.5% (95% CI: 41.1–71.1%). The response rate in group A was not significantly different from that in group B ($P = 0.671$).

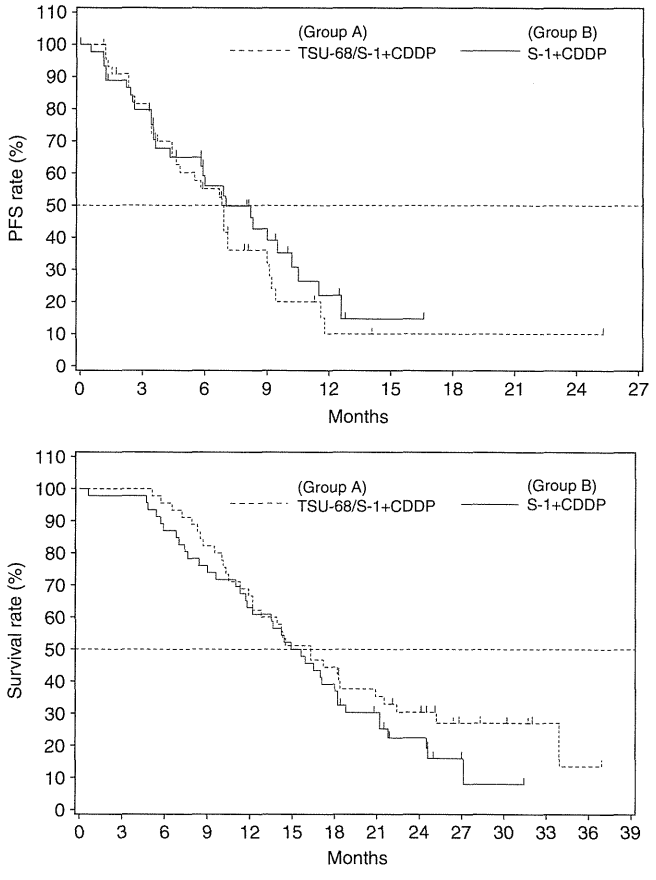

Figure 3. Kaplan–Meier analysis of PFS and OS. Of the 93 total patients, 46 were placed into group A and 47 were placed into group B. The median PFS times of the patients in group A and group B were 208.0 days (95% CI: 141.0–274.0 days) and 213.0 days (95% CI: 178.0–309.0 days), respectively. The HR for radiological progression or death in group A was 1.23 (95% CI: 0.74–2.05). The median OS times of the patients in group A and group B were 497.0 days (95% CI: 371.0–635.0 days) and 463.5 days (95% CI: 359.0–554.0 days), respectively. The HR for death in group A was 0.74 (95% CI: 0.46–1.19).

Safety. The AEs that occurred in this study are shown in Table 2. The main AEs that occurred at least 10% more frequently in group A than in group B were as follows: changes in the ALT, AST, and ALP levels, vomiting, diarrhoea, pigmentation abdominal pain, oedema, and urine colour change. The main AEs that occurred at least 10% less frequently in group A than in group B were as follows: neutropenia, changes in the leukocyte, TBIL, and creatinine levels, and stomatitis. The incidence rates of Grade 3 or higher AEs were the same in both groups; however, anorexia and changes in the haemoglobin and platelet levels occurred more frequently in group A than in group B. Specific changes observed in group A and group B patients were as follows: haemoglobin, 48.9% and 26.1%, respectively; platelet, 24.4% and 6.5%, respectively; anorexia, 17.8% and 8.5%, respectively.

In addition, no treatment-related deaths were noted in either group. Only 1 of the 46 patients (2.2%) in group B died within 90 days after enrolment, while only 2 (4.4%) died of aspiration and hypoxia during the study period.

Treatment continuity. The mean actual dose intensity of each drug in groups and B was as follows: S-1, 80.3% and 83.0%, respectively; CDDP, 89.6% and 92.0%, respectively; and TSU-68, 72.9% in group A. The median relative dose intensity (RDI) for S-1

Table 2. Incidence of adverse events

	Group A ($n=45$)						Group B ($n=46$)						
	Grade (n)						Grade (n)						P-value
	1	2	3	4	Total (%)	Grade 3< (%)	1	2	3	4	Total (%)	Grade 3< (%)	Any grade
Haemoglobin	7	8	21	1	82.2	48.9	6	17	12	0	76.1	26.1	0.607
Neutropenia	3	9	13	1	57.8	31.1	4	13	13	3	71.7	34.8	0.192
Platelets	16	7	6	5	75.6	24.4	25	5	2	1	71.7	6.5	0.813
Lymphocytes	8	7	8	0	51.1	17.8	4	12	6	0	47.8	13.0	0.835
Leukocytes	8	12	5	0	55.6	11.1	12	15	5	1	71.7	13.0	0.130
AST	14	6	2	0	48.9	4.4	15	1	0	0	34.8	0.0	0.205
ALT	13	3	2	0	40.0	4.4	10	2	0	0	26.1	0.0	0.185
ALP	14	5	0	1	44.4	2.2	10	0	0	0	21.7	0.0	0.027
T-Bilirubin	9	3	1	0	28.9	2.2	14	6	1	0	45.7	2.1	0.130
Albumin	12	12	3	0	60.0	6.7	16	13	0	0	63.0	0.0	0.831
Creatinine	10	1	0	0	24.4	0.0	16	2	0	1	41.3	2.1	0.119
Stomatitis	11	1	0	0	26.7	0.0	15	1	1	0	37.0	2.1	0.370
Anorexia	20	12	7	1	88.9	17.8	18	17	4	0	84.8	8.5	0.758
Nausea	23	12	0	0	77.8	0.0	21	15	1	0	80.4	2.1	0.801
Vomiting	17	8	0	0	55.6	0.0	10	9	0	0	41.3	0.0	0.211
Diarrhoea	16	7	5	0	62.2	11.1	15	7	2	0	52.2	4.3	0.399
Fatigue	19	14	2	1	80.0	6.7	27	8	3	0	82.6	6.4	0.793
Pigmentation	28	3	—	—	68.9	—	24	0	—	—	52.2	—	0.134
Abdominal pain	13	7	1	0	46.7	2.2	7	6	1	0	30.4	2.1	0.134
Oedema: All	19	7	0	0	57.7	0.0	11	1	0	0	26.1	0.0	0.003
Urine colour change	44	0	—	—	97.8	—	3	0	—	—	6.5	—	<0.001

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase. Adverse events were defined by the National Cancer Institute Common Terminology Criteria (version 3.0). Adverse events were compared with the use of Fisher's exact test. All reported P-values are two-sided.

was 85.6% in group A and 88.7% in group B. The median RDI for CDDP was 92.5% in group A and 92.9% in group B. Reasons for treatment discontinuation in groups A and B were as follows: PD, 69.6% and 78.7%, respectively; AEs (mainly bone marrow depression), 15.2% and 6.4%, respectively; withdrawal of consent, 4.3% and 4.3%, respectively; and indications for surgery, 10.9% and 4.3%, respectively. A total of 97.8% and 91.2% of patients in groups A and B, respectively, received second-line chemotherapy. At the end of the study, CPT-11-containing regimens were given to 37.8% and 42.9% of the patients in groups A and B, respectively, and taxane-containing regimens were given to 26.7% and 28.9% of the patients in groups A and B, respectively.

Subgroup analyses. Subgroup analyses of the patient backgrounds revealed no prolongation of PFS in any of the subgroups (Figure 4). In addition, neither the baseline nor the post-treatment measurements of the angiogenesis-related factors correlated with efficacy (data not shown).

Pharmacokinetics. The pharmacokinetic parameters of TSU-68, S-1, and CDDP are shown in Table 3.

The mean maximum drug concentration (C_{max}) and the area under the curve of the plasma concentration *vs* time from 0 to the final time point (AUC_{0-last}) for TSU-68 were 4.46 $\mu g\,ml^{-1}$ and 23.23 $\mu g\,h^{-1}\,ml^{-1}$, respectively. These values were not significantly different from the previously reported results for TSU-68 monotherapies and combination therapies (Kanai *et al*, 2010; Murakami *et al*, 2011; Ueda *et al*, 2011; Okamoto *et al*, 2012; Toi *et al*, 2012).

For S-1, the C_{max} and AUC_{0-last} of the FT were significantly lower in group A than in group B, and the half-life ($t_{1/2}$) was significantly shorter in group A than in group B. However, no significant difference was noted between the two groups with regard to the C_{max} or the AUC_{0-last} of 5-FU. The AUC_{0-last} of CDHP and Oxo were significantly lower in group A than in group B.

For CDDP, the C_{max} and the AUC_{0-last} of free platinum were significantly lower in group A than in group B.

DISCUSSION

The median PFS was 208.0 days (95% CI: 141.0–274.0 days) in group A and 213.0 days (95% CI: 178.0–309.0 days) in group B.

According to the Central Imaging Review Committee, none of the patients in either group achieved a complete response. A total of 28 patients in group A and 26 patients in group B achieved a PR. The response rate was 62.2% (95% CI: 46.5–76.2%) in group A and 56.5% (95% CI: 41.1–71.1%) in group B. No additional TSU-68 effect was demonstrated.

The median survival period was 497.0 days (95% CI: 371.0–635.0 days) in group A and 463.5 days (95% CI: 359.0–554.0 days) in group B. Beyond the median point, differences in the survival

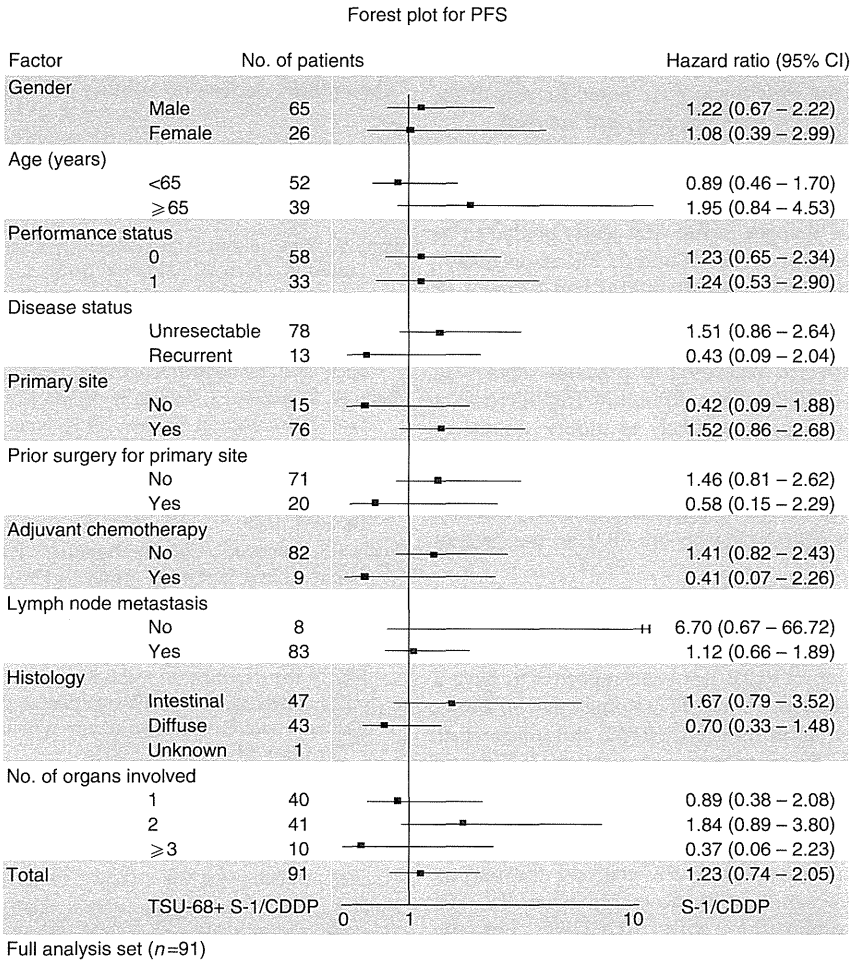

Figure 4. Forest plot for PFS. No prolongation of PFS was observed in any of the subgroups.

Table 3. Pharmacokinetic (PK) parameters

			PK parameters			
	Group	No. of patients	t_{max} (h)	C_{max} ($\mu g\,ml^{-1}$)	AUC_{0-last} ($\mu g\,h^{-1}\,ml^{-1}$)	$t_{1/2}$ (h)
TSU-68	A	6	3.5 ± 1.5	4.46 ± 0.95	23.2 ± 7.0	2.2 ± 0.7
S-1						
FT	A	12	2.3 ± 0.8	2168 ± 378**	13 368 ± 2581**	6.9 ± 1.1**
	B	12	2.4 ± 1.2	3693 ± 1309	29 219 ± 10 288	13.3 ± 4.4
5-FU	A	12	3.1 ± 0.7	202 ± 65	891 ± 315	1.6 ± 0.3**
	B	12	3.8 ± 1.2	160 ± 37	976 ± 221	2.4 ± 0.6
CDHP	A	12	2.6 ± 0.8	228 ± 55	993 ± 229**	2.9 ± 0.6*
	B	12	2.7 ± 1.1	263 ± 94	1442 ± 337	3.8 ± 0.8
Oxo	A	12	3.3 ± 1.8	44 ± 22*	258 ± 133*	3.2 ± 0.9
	B	12	3.0 ± 1.7	90 ± 59	498 ± 285	4.6 ± 2.3
CDDP						
Free platinum	A	6	1.7 ± 0.5	1277 ± 169*	2813 ± 360*	0.783 ± 0.071
	B	7	2.0 ± 0.0	1585 ± 284	3441 ± 437	0.819 ± 0.070

Abbreviations: CDHP = 5-chloro-2,4-dihydroxypyridine; FT = 5-fluoro-1-(tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (tegafur); 5-FU = 5-fluorouracil; Oxo = monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate (oxonic acid). Mean ± s.d. *P-value <0.05; **P-value <0.001.

curve indicated that a small number of patients in group A tended to have prolonged survival; however, per the stratified analyses, no correlation with efficacy was observed.

No statistically significant differences were noted for any of the endpoints, which included PFS, response rate, and survival.

With regard to the safety profile, no significant difference was observed in the AE incident rates between the groups, except for changes in ALP levels, oedema, and urine colour change (Table 2). Although the incidence of changes in the ALP levels tended to be higher in group A than in group B (44.4% and 21.7%, respectively), most of these patients with ALP level alterations had Grade 1 or Grade 2 AEs. OEdema and urine colour change are typical AEs of TSU-68, and almost of them were not severe and controlled enough. All AEs were expected according to previous reports on AEs for TSU-68, TS-1, and CDDP. The addition of TSU-68 to TS-1 plus CDDP, a standard therapy, is unlikely to induce serious or fatal events.

On the other hand, although the evaluation of the quality of life (QOL) was recently determined to be important in the evaluation of tolerability, we did not collect data on the QOL in the present study.

From the results of the TSU-68 PK profile in group A, S-1 and CDDP are unlikely to influence the PK of TSU-68. The induction of FT metabolism by TSU-68 could be a reason for the decreased AUC of FT in group A, as CYP1A2 has been reported to have a minor role in the metabolism of FT to 5-FU (Komatsu *et al*, 2000), and TSU-68 has the potential to induce CYP1A2 (Kitamura *et al*, 2008). The effects of TSU-68 on plasma exposure to CDHP and Oxo cannot be denied; however, TSU-68 had no effect on plasma exposure to 5-FU, the active ingredient of S-1. Therefore, combination therapy with TSU-68 was unlikely to affect the efficacy or safety of S-1. In the CDDP PK analysis, the plasma exposure to free platinum significantly decreased when TSU-68 was administered in combination with S-1/CDDP, but the degree of this decrease was not remarkable (~20%). The effect of this slight decrease in platinum exposure on the efficacy and safety of CDDP is unknown. Therefore, further studies are required to investigate the interaction between TSU-68 and CDDP.

Molecular target therapies are increasingly being developed for the treatment of gastric cancer. Trastuzumab was found to induce a substantial increase in OS in HER-2-positive patients with metastatic gastric cancer when combined with chemotherapy (Bang *et al*, 2010). The antiangiogenic agent bevacizumab, in combination with capecitabine and cisplatin as a first-line therapy, significantly improved the PFS rate and ORR; however, no survival benefit related to this drug was noted (Ohtsu *et al*, 2011). Ramucirumab significantly prolonged OS when used as a second-line monotherapy (Fuchs *et al*, 2013). An understanding of past studies of molecular target agents is necessary for appropriate patient selection.

Taken together, our results show that a combination therapy that comprised TSU-68, TS-1, and CDDP was safe and well tolerated in patients with unresectable or recurrent gastric cancers. However, TSU-68 did not demonstrate the expected enhanced efficacy. Further studies to explore all aspects that affect efficacy are necessary.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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