Table 4 The incidence of grade 3 or 4 adverse events (%)

	Present study		SPIRITS trial	
	SP group ($n = 21$)	S-1 group ($n = 37$)	SP group ($n = 148$)	S-1 group ($n = 150$)
Hematological				
Leukocytopenia	28.6	2.7	11	2
Neutropenia	33.3	5.4	40	11
Anemia	42.9	32.4	26	4
Thrombocytopenia	19.0	0	5	0
Non-hematological				
Febrile neutropenia	0	0	3	1
Fatigue	9.5	13.5	4	1
Anorexia	14.3	13.5	30	6
Diarrhea	4.8	0	4	3
Stomatitis	0	2.7	0.7	0
Nausea	4.8	5.4	11	1
Vomiting	0	0	4	2

the S-1 group. Chemotherapy in both treatment groups was discontinued due to disease progression in many patients. It was evident that both treatments were feasible even in elderly patients.

The incidence of grade 3 or higher adverse events in the present study was more frequent than in the SPIRITS trial (Table 4), which could possibly be attributed to decreased creatinine clearance. In this study, patients with poor renal function experienced more severe adverse events. The pharmacokinetics of S-1 are dependent on renal function because 5-chloro-2,4-dihydroxypyridine, which is an inhibitor of dihydropyrimidine dehydrogenase [12–17], is eliminated through the kidneys. Organ functions, including renal function in the elderly, are likely to be somewhat impaired, and it has been reported that the glomerular filtration rate generally decreases with age [18]. The decreased creatinine clearance might lead to more frequent and severe toxicities associated with S-1, especially in elderly patients. Therefore, it is necessary to consider renal function before starting S-1-based chemotherapy, especially in elderly patients.

In geriatric oncology, neither the Karnofsky Performance Scale Index nor ECOG PS may be reliable for assessing physical status because comorbidities in elderly patients might affect their physical or mental status [19]. It has been reported that assessment of the condition of elderly cancer patients measured by comprehensive geriatric assessment (CGA) is useful for predicting tolerance to chemotherapy and survival [20–22]. CGA is a multidimensional evaluation scale of an elderly patient's physical performance, comorbidity, cognition, psychological stage, socioeconomic status, nutritional status, and medications [23, 24]. In some clinical trials targeting elderly cancer patients, functional assessment scales were adopted for patient selection in addition to PS and organ function assessments [25, 26]. In this study, PS was the only factor associated with survival. In addition, CGA might interfere with measurement of PS, as demonstrated in previous studies [20, 24, 27]. Thus it is suggested that CGA might also affect the clinical outcomes, especially the survival rates, of gastric cancer patients treated with chemotherapy.

In conclusion, SP therapy and S-1 monotherapy were both feasible in elderly patients with AGC, though the superiority of SP therapy over S-1 monotherapy was not so prominent in this review. Further clinical trials are warranted to establish a new standard care, especially in elderly gastric cancer patients.

Conflict of interest No author has any conflict of interest.

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進行再発胃癌に対する化学療法の現況と展望

樋口　勝彦，小泉　和三郎

北里大学医学部消化器内科学

日本では胃癌は肺癌に次ぎ，癌による死因の第2位である。進行・再発胃癌に対する化学療法は過去に行われた第III相臨床試験の結果，標準的治療が確立され，治療成績が向上してきた。それにより日本ではS-1 + cisplatin療法が標準的治療として確立された。さらにはDCS療法といった3剤併用療法への期待も高まっている。近年，分子標的薬剤の開発が進み，HER2陽性の進行胃癌に対するtrastuzumabの上乗せ効果がglobal試験で証明された。この結果，胃癌の領域でも個別化治療の幕が開けた。今後，新たなバイオマーカーの研究が進み，個別化治療に関する新たな治療戦略が開発されることが期待される。

Key words: 胃癌，化学療法，分子標的薬剤，個別化治療

緒　言

胃癌は2008年の統計において肺癌，乳癌，大腸癌につぎ，世界で4番目の悪性腫瘍 (989,000症例，全体の7.8%) である。また，胃癌は，世界中の癌死の中で第2の主要な死因である (死亡者数738,000人，全体の9.7%)。最も死亡率が高いのは東アジア (男性10万人につき28.1人，女性10万人につき13.0人) であり，最も死亡率が低いのは北アメリカ (それぞれ2.8人と1.5人) とされている[1]。日本では，発見数では最も多い癌種であり，年間死亡数は肺癌につぎ2位である。

進行・再発胃癌に対する化学療法は過去に行われてきた第III相臨床試験の経緯や各国間の医療保険制度，薬剤の承認状況の相違などから欧米と日本では標準的治療が異なっている。日本においては標準的化学療法が確立されていなかったが，2007年から相次いで大規模な無作為化第3相比較試験の結果が報告され，cisplatin (CDDP) + S-1 (CS) 療法が標準的治療として確立された[2,3]。さらにはHER2陽性の進行胃癌に対しtrastuzumabの上乗せ効果がglobal試験で証明された[4]。この総説では世界と日本における近年の胃癌化学療法の進歩と将来展望に関し解説する。

1990年代までの臨床試験の結果

胃癌における化学療法の歴史は長いものの，evidenceに乏しいといわれ言われ続けてきた。しかし，新薬の開発，併用療法の進歩とともに徐々にでは

表1. 化学療法とbest supportive care (BSC) の比較試験

研究者	レジメン	患者数	奏功率 (%)	MST (月)	P value
Murad[5]	FAMTX	30	50	9	0.001
	BSC	10		3	
Scheithauer[6]	ELF	10	30	10	<0.02
	BSC	8		4	
Pyrhonen[7]	FEMTX	21	29	12.3	0.0006
	BSC	20		3.1	

MST, median survival time (生存期間中央値); FAMTX, 5-FU + doxorubicin + methotrexate; ELF, etoposide + leucovorin + 5-FU; FEMTX, 5-FU + epirubicin + methotrexate

Received 28 December 2011, accepted 13 February 2012
連絡先: 樋口勝彦 (北里大学医学部消化器内科学)
〒252-0380 神奈川県相模原市南区麻溝台2-1-1
E-mail: k.higu@kitasato-u.ac.jp

あるが大規模な臨床試験が行われるようになり，奏効率や予後の改善がみられる様になった。

1990年代に併用化学療法とbest supportive care (BSC)との比較試験が発表され，表1に示すように3つの試験でBSC群に対し併用化学療法群で有意な延命効果が確認された[5-7]。つまり，進行胃癌に対する化学療法の意義が証明されたわけである。

しかし，この時代においては世界で数多くの臨床試験が行われ，有望とされる様々なレジメンが検証されたが，標準治療の確立までは至らなかった。その中でCDDPと5-fluorouracil (5-FU) との併用療法 (CF療法) は複数の比較試験で試験治療として検証されてきた。その結果を表2に示す。Kimらが報告した5-FU単独療法とCF療法，5-FU + doxorubicin + mitomycin C (FAM療法) との3群比較では，全生存期間 (overall survival: OS) は3群で差はないものの，奏効率，無増悪期間 (time to progression: TTP) においてCF療法群が他の2群と比較して有意に良好であった[8]。その後，Vanhoeferが報告し

表2. CF療法に関する第3相試験の結果

研究者	レジメン	患者数	奏効率 (%)	P value	PFS	P value	MST	P value
Kim[8]	5-FU	102	26	<0.01	9.1 W*	<0.01	30.6 W	NS
	CF	112	51	<0.01	21.8 W*	<0.01	36.9 W	
	FAM	110	25		12 W*		29.3 W	
Vanhoefer[9]	ELF	132	9	NS	3.3 M	NS	7.2 M	NS
	CF	134	20		4.1 M		7.2 M	
	FAMTX	133	12		3.3 M		6.7 M	
JCOG9205[10]	5-FU	105	11	<0.001	1.9 M	<0.001	7.1 M	NS
	CF	105	34		3.9 M		7.3 M	
	UFT-M	70	9		2.4 M		6.0 M	

CF, cisplatin + 5-FU; PFS, 無増悪生存期間; FAM, 5-FU + doxorubicin + mitomycin C; NS, 有意差なし; UFT-M, tegafur/uracil + mitomycin C
*無増悪期間

表3. 最近の世界における第3相試験の結果

試験名	レジメン	患者数	奏効率 (%)	PFS (月)	P value	MST (月)	P value
V-325[11]	CF	224	25	3.7**		8.6	
	DCF	221	37	5.6**	<0.001	9.2	0.02
REAL2[12]	ECF	263	41	6.2		9.9	
	EOF	245	42	6.5		9.3	
	ECX	250	46	6.7		9.9	
	EOX	244	48	7.0	NS	11.2	非劣性***
ML17032[13]	CF	137	29	5.0		9.3	
	CX	139	41	5.6	非劣性	10.5	非劣性
FLAGS[14]	CF	508	31.9	5.5		7.9	
	CS	521	29.1	4.8	NS	8.6	NS
ToGA[4]	CX*	290	34.5	5.5		11.1	
	CX* + trastuzumab	294	47.3	6.7	0.0002	13.8	0.0046
AVA-GAST[15]	CX*	387	37	5.3		10.1	
	CX* + bevacizumab	387	46	6.7	0.0037	12.1	NS

DCF, docetaxel + cisplatin (CDDP) + 5-FU; ECF, epirubicin + CDDP + 5-FU; EOF, epirubicin + oxaliplatin (L-OHP) + 5-FU; ECX, epirubicin + CDDP + capecitabine; EOX, epirubicin + L-OHP + capecitabine; CX, CDDP + capecitabine; CS, CDDP + S-1
*CDDP + capecitabine or 5-FU, **無増悪期間, ***5-FUに対するcapecitabineの非劣性 とCDDPに対するL-OHPの非劣性。EOX群ではECF群に比べ有意に生存期間が延長 (P = 0.02)

たetoposide + leucovorin + 5-FU (ELF) とCFと5-FU + doxorubicin + methotrexate (FAMTX) の比較試験では，3群間でOS，奏効率，無増悪生存期間 (progression-free survival: PFS) において差は認められなかった[9]。この時点では有意に生存期間を延長させる標準治療は確立されなかったが，比較的高い安全性や奏効率，PFSの点から欧米や韓国の実臨床ではCF療法が汎用されるようになった。結果，CF療法はその後の数多くの第III相臨床試験においてreference armとして採用されることになった。

日本においても1990年代，日本臨床腫瘍グループ (Japan Clinical Oncology Group: JCOG) で5-FU単独療法とCF療法，tegafur/uracil + mitomycin C (UFT-M) を比較する大規模な第III相臨床試験，JCOG9205が行われた[10]。CF療法は奏効率とPFSにおいて5-FU単独療法より良好であったが，OSには差が見られなかった。安全性は5-FU単独療法で高く，JCOGは次の第III相試験のreference armとして5-FU単独療法を採用した。ここで海外と日本におけるreference armの考え方に違いが生じたのである。

21世紀の海外における進行胃癌に対する化学療法の進歩

21世紀になり，立て続けに大規模比較試験における有意な結果が報告されるようになった (表3)。2005年の米国臨床腫瘍学会 (ASCO) の総会においてV325試験の最終結果が報告された[11]。この試験ではCF療法 (cisplatin 100 mg/m^{2}をday 1に点滴静注，5-FU 1,000 mg/m^{2}をday 1～5に持続静注，4週毎に繰り返す) がreference armとして用いられた。457人の初回化学療法患者がDCF療法 (docetaxel 75 mg/m^{2}をday 1に点滴静注，cisplatin 75 mg/m^{2}をday 1に点滴静注，5-FU 750 mg/m^{2}をday 1～5に持続静注，3週毎に繰り返す) またはCF療法に無作為に割り付けされた。TTP，OS，奏効率は，CF群と比較して，DCF群で有意に良好であった。治療に関連したGrade 3以上の有害事象はCF療法に比べDCF療法で頻度が高く (81%対75%)，特に好中球減少はDCFで頻度が高かった (82%対57%)。この結果，DCF療法は毒性の管理が必要であるが，進行胃癌に対する新しい治療選択の一つであると結論付けられた。現在，DCFの毒性を軽減し，安全性，継続性を高めることを目的にDCFのmodificationが試みられている。

REAL2試験はECF (epirubicin/CDDP/5-FU) をstandard armとし，EOF (epirubicin/oxaliplatin (L-OHP)/5-FU)，ECX (epirubicin/CDDP/capecitabine) またはEOX (epirubicin/L-OHP/capecitabine) の3 armをtest armとした試験であり，5-FU群対capecitabine群と，CDDP群対L-OHP群の非劣性を比較した2 × 2デザインで行われた[12]。capecitabine群の5-FU群に対するOSのハザード比 (hazard ratio: HR) は0.86 (95% CI，0.8～0.99) であり，L-OHP群のCDDP群に対する全生存期間のHRは0.92 (95% CI 0.80～1.10)であった。結果，5-FUに対するcapecitabineの非劣性が証明され，CDDPに対するL-OHPの非劣性が証明された。さらに，副次的解析において，EOX群のECF群に対するOSのHRは0.80 (95% CI，0.66～0.97; P = 0.02) であり，EOX群で有意に生存期間の延長が見られた。

アジア，ラテンアメリカ，東欧諸国で行われたML17032試験は，CF療法に対するCDDP + capecitabine (CX) 療法の非劣性を比較した第III相臨床試験である[13]。Primary endpointであるPFSにおいて，それぞれCX群5.6か月，CF群5.0か月であり，CF療法に対するCX療法の非劣性が証明された。有害事象に関しては，CX群でhand-foot症候群 (HFS) の頻度が高かったが (22%対4%)，嘔吐 (59%対49%)，口内炎 (26%対12%) に関してはCF群の方が高頻度であった。これにより前述のREAL2試験の結果とあわせて，capecitabineの効果は5-FUと同等以上であると考えられ，さらにCX療法が進行胃癌に対する新しい治療選択の一つであると結論付けられた。

ASCO Gastrointestinal Cancers Symposium 2009でCF療法とCS療法を比較したFLAGS試験が発表された[14]。primary endpointであるOSに関してはCF群のMST 7.9か月に対し，CS群8.6か月とS-1 + CDDP療法群で良好な傾向を認めたが，有意差は認めなかった (HR，0.92; 95%のCI，0.80～1.05; P = 0.20)。奏効率，PFSに関しても両群で有意差がみられなかった。有害事象に関してはCS群で有意に安全性が高く，grade 3以上の好中球減少 (32.3%対63.6%)，好中球減少症を伴う発熱または感染 (5.0%対14.4%)，口内炎 (1.3%対13.6%)，低カリウム血症 (3.6%対10.8%)，治療関連死 (2.5%対4.9%; P = 0.05) の頻度が低かった。

ASCO 2009ではさらにCSのCFに対するOSに関しての非劣性の解析と組織型別のsubset analysisの追加解析結果が報告された。非劣性マージンの設定においては過去の他の試験やmeta-analysisの結果からHR = 1.10が妥当と判断され，本試験のHRの上限値が1.10を下回っていたことから非劣性が有意に証明された。さらに組織型がdiffuse typeであるsubsetでは，HR = 0.83，P = 0.0413と有意にCS群が良好な結果が示された。演者らは，CSがCFの最適な代替治療であり，diffuse typeでの高い効果を明らかにするための追加試験を行う価値があると結論した。この試験の結果，TS-1はCDDPとの併用で進行胃癌に対する初回治療として2011年3月に欧州で承認された。

ASCO 2009でHER2陽性進行胃がんを対象としHER2に対するモノクローナル抗体であるtrastuzumabの有効性を検証したToGA試験の結果が報告された[4]。本試験は，胃がん領域で初めて行われた分子標的薬の第III相

臨床試験であった。コントロール群はCFあるいはCXで，trastuzumab群はCFあるいはCXにtrastuzumabを併用とし，primary endpointはtrastuzumab群のOSでの優越性と設定された。HER2のスクリーニングは中央診断によるimmunohistochemistry (IHC) およびFISH法にて行われ，IHC3+あるいはFISH陽性例を適格とした。24か国が参加し，地域別では日本を含むアジア55%，欧州33%，中南米9%，その他3%であった。食道胃接合部がんが18%含まれ，組織型別ではintestinal typeが75%であった。Primary endpointであるOSの比較では，MSTがコントロール群11.1か月，trastuzumab群13.8か月，HR = 0.74 (95% CI: 0.60～0.91)，P = 0.0046と有意にtrastuzumabによる有意な生存期間の延長が証明された。PFS，奏効率も有意にtrastuzumab群が上回った。HER2の発現程度によるsubset analysisでは，IHC2+/FISH陽性あるいはIHC3+の症例 (n = 446) で，MSTが11.8か月対16.0か月，HR = 0.65 (95% CI: 0.51～0.83) とその差がより顕著であった。毒性においては両群間に差はなく，無症候性の左室駆出率の低下がtrastuzumab群で5.9%と高かったが，心血管系のイベントには両群に差がみられていない。以上から，HER2陽性胃がんに対してtrastuzumab + 化学療法の併用は標準治療の1つとなった。

本試験は，胃がんに対して初めて分子標的薬の有効性を示した試験であり，乳がんと同様にHER2陽性例という独立したグループを確立させることになるなど大きな意義をもつ。乳がんに続いてのtrastuzumabの成功は，personalized therapyの方向性をより促進するであろう。

ASCO 2010でVEGFに対するモノクローナル抗体であるbevacizumabの有効性を検証したAVAGAST試験の結果が報告された[15]。この試験は日本，韓国が中心となったglobal試験で，CXに対するbevacizumabの上乗せ効果を検証する目的で計画されたランダム化二重盲検プラセボ対照第III相臨床試験であった。実際の登録症例は日本と韓国で全体の40%以上を占めた。Primary endopointはOSで，プラセボ群とベバシズマブ併用群でMST 10.1か月対12.1か月 (HR : 0.87，P = 0.1002) であり，両群に有意差を認めなかった。OSに関するsubanalysisでは，地域別に生存期間中央値を検討した場合，アジア (プラセボ群vs.ベバシズマブ併用群) 12.1か月対13.9か月 (HR : 0.9)，欧州8.6か月対11.1か月 (HR : 0.85) と有意差を認めなかったのに対し，アメリカでは6.8か月対11.5か月 (HR : 0.63) と有意差を認めた。地域別の2次治療移行率は，アジア66%，欧州31%，アメリカ21%であった。AVAGAST試験の結果はnegativeであり，全世界の研究者に失望感を与え，global試験の難しさを認識させる結果となった。

21世紀の日本における進行胃癌に対する化学療法の進歩 (表4)

JCOG9205の次に行われたJCOG9912は，5-FU単独群に対するCPT-11 + CDDP療法群の優越性とS-1療法群の非劣性を検証した3 armの第III相臨床試験である[2]。Primary endpointはOSであり，MSTは5-FU療法が10.8か月であったのに対して，CPT-11 + CDDP療法が12.3か月 (P = 0.055)，S-1単独療法が11.4か月 (非劣性P < 0.001) であった。結果，CPT-11 + CDDP療法の優越性は示せなかったものの，S-1療法の非劣性が証明された。

当時，S-1はAGCに対する第一選択の化学療法として，日本で広く使われていた。第II相試験おけるS-1併

表4. 最近の日本における第3相試験の結果

試験名	レジメン	患者数	奏効率 (%)	PFS (月)	P value	MST (月)	P value
JCOG9912[2]	5-FU	234	9	2.9		10.8	
	CPT-11 + CDDP	236	38	4.8	<0.0001	12.3	NS
	S-1	234	28	4.2	0.0027	11.4	非劣性*
SPIRITS[3]	S-1	150	31	4.0		11.0	
	S-1 + CDDP	148	54	6.0	<0.0001	13.0	0.04
TOP-002[16]	S-1	160	27	3.6**		10.5	
	S-1 + CPT-11	155	42	4.5**	NS	12.8	NS
ISO-5FU10[17]	S-1	88	29.5	3.5		8.3	
	5-FU + l-LV	89	23.6	4.0	非劣性	10.3	非劣性
START[18]	S-1	313	18.4	4.1***		11.0	
	S-1 + docetaxel	310	30.3	5.3***	<0.001	12.8	NS

MMC, mitomycin C; CPT-11, irinotecan; l-LV; l-leucovorin
*5-FUに対する非劣性，**治療成功期間，***無増悪期間

用療法の有望な結果に基づいて，3つの第III相試験 (SPIRITS, TOP-002, START) が，S-1単独療法とS-1併用療法とを比較する目的で行われた。

SPIRITS試験は，S-1単独療法に対するCS療法の優越性を検証する第III相試験である[3]。CS療法はS-1 80 mg/m²をday 1～21に内服し，CDDPをday 8に60 mg/m²点滴静注し，5週毎に繰り返すものである。Primary endpointはOSであり，MSTはS-1単独群が11.0か月に対し，CS群が13.0か月 (P = 0.0366) と有意な延長を示した。また，PFS，ORRに関しても，S-1単独群に比べCS群で有意に良好であった。

白血球減少症，好中球減少，貧血，悪心，食欲不振などのGrade 3以上の有害事象は，S-1単独群よりもCS群で高率であった。治療関連死は両群で発生しなかった。JCOG9912試験とSPIRITS試験の結果，CS療法は日本における切除不能進行・再発胃癌患者に対する標準的初回化学療法となった。胃癌治療ガイドラインの中でも，切除不能進行・再発例に対する初回治療としてCS療法は推奨されている。

S-1単独療法とS-1 + CPT-11療法を比較した第III相試験 (TOP-002) が行われたが，primary endpointであるOSにおいて，S-1単独療法のMST 10.5か月に対しS-1 + CPT-11療法は12.8か月であり，有意差は示せなかった (P = 0.23)[16]。

切除不能進行・再発胃癌患者におけるS-1単独療法に対するI-ロイコボリン + 5-FU (RPMI) 療法の非劣性を検討した第3相試験 (ISO-5FU10) が2009年に報告された[17]。Primary endpointであるOSにおいて，S-1単独療法のMST 8.3か月に対し，RPMI療法は10.3か月で，ハザード比は0.84 (95% CI: 0.60～1.18) となり，S-1単独療法に対するRPMI療法の非劣性が示された。また，PFSに関しても，S-1単独療法のPFS中央値3.5か月に対し，RPMI療法は4.0か月で，ハザード比は0.76 (95% CI: 0.55～1.06) であった。安全性と患者のQOLに関しては両群で差はなかった。経静脈投与であるRPMI療法はS-1療法の代替療法になりえると考えられ，特に原疾患により経口摂取ができない患者が良い適応になるだろう。

ASCO Gastrointestinal Cancers Symposium 2011でS-1単独療法とdocetaxel + S-1療法を比較した第III相試験 (START) 発表された[18]。Primary endpointであるOSにおいて，DS群のMSTが12.8か月に対し，S-1単独群では11.0か月と，DS療法の優越性は示されなかった (P = 0.142)。サブセット解析では，標的病変のない症例では，DS療法のMST (17.2か月) がS-1療法のMST (11.5か月) に比べ有意に優っていた (HR = 0.674; 95% CI: 0.465～0.977)。同様にリンパ節転移のない症例では，リンパ節転移のある症例に比べ，DS療法はS-1療法に有意に優っていた (HR = 0.662; 95% CI: 0.476～0.920)。この結果から，DS療法はCS療法と同様に，明らかなリンパ節転移や標的病変を伴わない腹膜播種型に有効である可能性がある。

将来展望

1. 日本で現在進行中の第III相臨床試験

日本では胃癌に対し，L-OHPが保険適応として承認されていない。Phase II studyにおいてS-1 + L-OHP (SOX) 療法は優れた治療成績を示した[19]。そのため，胃癌に対するL-OHPの承認を目指し，CS療法に対する

表5. 現在進行中の分子標的薬剤に関する第3相試験

試験名1	標的	対象	参加地域	盲検性	目標患者数	主要エンドポイント	レジメン
REAL 3	EGFR	初回治療	英国	Open label	730	OS	EOX EOX + panitumumab
EXPAN	EGFR	初回治療	Global	Open label	870	PFS	CX CX + cetuximab
LOGiC	HER-2	初回治療	Global	Double blind	410	PFS	OX* OX + lapatinib
TYTAN	HER-2	2次治療	アジア	Open label	314	OS	Paclitaxel Paclitaxel + lapatinib
RAINBOW	VEGFR-2	2次治療	Global	Double blind	663	OS	Paclitaxel Paclitaxel + ramucirumab
GRANITE-1	mTOR	2，3次治療	Global	Double blind	633	OS	Placebo RAD001 (everolimus)

OS, 全生存期間; OX, oxaliplatin + capecitabine

SOX療法の非劣性を検証する第III相臨床試験が現在進行中で，症例登録は既に終了している。Primary endpointはPFSとOSであり，今後の解析結果が待たれる。

2. 日本における3剤併用化学療法

欧米ではECF療法やDCF療法といった3剤併用療法が初回化学療法の標準治療として位置づけられている。日本においてはCS療法が標準的治療法であるが，docetaxel + CDDP + S-1 (DCS) 療法が標準療法の新たな候補として期待されている。

日本からDCS療法のPhase II studyが3つ報告されている[20-22]。北里大学消化器内科と神奈川県立がんセンター消化器内科で共同開発したKDOG regimenはdocetaxel 40 mg/m^{2}をday 1に点滴静注，Cisplatin 60 mg/m^{2}をday 1に点滴静注，S-1 80 mg/m^{2}をday 1から2週間内服投与し4週毎に繰り返す治療法である。切除不能進行・再発胃癌患者における第II相臨床試験の結果，奏効率81.3%，median PFS 8.7か月，MST 18.5か月と優れた有効性が示された。このKDOG regimenは3剤併用療法で最も危惧される骨髄毒性をはじめとした有害事象の軽減が計られ，術前化学療法に関する多くの臨床試験において，試験治療として採用されている。さらには切除不能進行・再発胃癌患者を対象としたCS療法との第III相比較試験 (JCOG1013) で試験治療としての採用が決定され，今後の動向が注目されている。

3. 分子標的治療

現在，進行胃癌を対象にpanitumumab，cetuximab，lapatinib，ramucirumab，everolimus (RAD001) に関する第III相比較試験が進行中であり，日本はその中で重要な役割を担っている。初回治療例を対象としてEOXにEGFRに対するモノクローナル抗体であるpanitumumabを上乗せするREAL-3が英国で行われている。同じくEGFRに対するモノクローナル抗体であるcetuximabに関しては初回治療例を対象にCXへの上乗せ効果を検証するEXPANDがglobal studyとして進行中である。HER 1/2 dual inhibitorであるlapatinibの比較試験が，初回治療ではcapecitabine + oxaliplatinの併用 (LOGiC) で，二次治療ではパクリタキセルとの併用(TYTAN)で進行している。乳がん同様のHER2陽性例への治療戦略が胃がんでも応用されていくものと予想される。VEGFR-2を標的とするramucirumabの比較試験が，二次治療例を対象にパクリタキセルとの併用で進行している (RAINBOW)。また，2次治療，3次治療例を対象にmTOR阻害剤であるeverolimusとplaceboとの二重盲検無作為化比較試験が進行中である (GRANITE-1)。これらの大規模試験の結果，trastuzumabのように，胃癌で有効性を示す新たな分子標的薬剤が誕生するか大いに注目される。

4. 個別化治療

現在，個別化治療は，分子標的薬剤を開発する上で非常に重要な課題である。他の癌腫に比べて胃癌では予後予測因子や効果予測因子となる有意なbiomarkerの報告は少ない。ToGA試験でHER2陽性の進行胃癌患者における生存期間に関するtrastuzumabの上乗せ効果が示された。本邦においても，この結果に基づきtrastuzumabが保険適応として承認され，HER-2陽性例はtrastuzumabの投与が標準治療となった。さらに乳癌において，trastuzumab耐性のHER2陽性の乳癌に対するlapatinibの有効性が示されており，現在胃癌においても，初回治療例と2次治療例に対するlapatinibの第III相臨床試験が進行中である。しかし，胃癌においてはHER-2の陽性率は13～22%と決して高くなく，今後，HER-2以外の有力なbiomarkerの探索が望まれる。

有力なbiomarkerとして胃癌の組織型が候補として注目されている。前述のFLAGS試験において，組織型がdiffuse type (日本における低分化腺癌や印鑑細胞癌にあたる) であるsubsetでは，CS群がCF群に比べ良好な結果が示された。現在，diffuse typeの進行胃癌患者を対象に，CF療法に対するCS療法の生存期間における優越性を検証するDIGEST試験が米国を中心に展開中である。

我々は初回治療としてS-1単独療法かCS療法が行われた患者120例の胃癌組織を用い，5-FUに関連した薬物代謝酵素のmRNAを測定することにより，mRNAの発現状況と予後との関係をretrospectiveに検討した[23]。S-1単独療法で治療を行った患者において，多変量解析の結果，TP低発現，TS低発現，OPRT高発現は有意な予後予測因子であった。さらに，TP，TS共に低発現の患者においてはCS療法群よりもS-1単独療法群で有意に予後が良好であり，有害事象の発現頻度もS-1単独療法群で低い傾向にあった。これらのバイオマーカーはS-1単独療法でも十分な効果が期待される患者を抽出することに有用かもしれない。しかし，retrospective studyにおいて確認されたバイオマーカーの有用性は，今後，prospective studyでの検証が必要であろう。

5. 二次化学療法

ASCO 2009で胃がん二次治療におけるCPT-11 aloneとBSCとの無作為化比較試験の結果がドイツのAIOグループより報告された[24]。目標症例数120例であったが，症例集積が進まず40例の段階で試験は中止された。Primary endpointはOSで，MSTがBSC群73日，CPT-11群123日，HR = 0.48 (95% CL 0.25～0.92)，P = 0.023と有意にCPT-11による生存期間の延長が証明された。本試験は，試験途中で中止され症例数が少ないなどの問題があるが，胃がん化学療法で初めて二次治療およびイリノテカンの有効性を比較試験で示唆した点で意義深い。また，ASCO2011で二次治療におけるBSCと

化学療法 (CPT-11またはdocetaxel) の比較試験の結果が韓国から報告され，化学療法群で生存期間の延長が示された。

現在，二次治療における標準治療は確立されていないため，日本ではweekly paclitaxelやCPT-11単独，CPT-11 + CDDPが二次治療として汎用されている。現在，これら二次治療に関する比較試験が複数進行中であり，その結果が期待される。

まとめ

進行・再発胃癌に対する化学療法は過去に行われてきた臨床試験の結果，標準的治療が確立され，治療成績が向上してきた。その結果，欧米ではCX療法やECF，DCFが標準的治療として位置づけられた。日本においてはcapecitabineが承認されていなかったため，S-1を中心とした併用療法の開発が進み，CS療法が標準的治療となった。近年，CX療法に対する分子標的薬剤の上乗せを評価したglobal試験に参加することにより，日本でもcapecitabineとtrastuzumabが承認された。また，3剤併用療法であるDCS療法は第II相試験において優れた治療効果を示し，術前化学療法の応用や切除不能進行・再発胃癌患者を対象としたCS療法との第III相比較試験 (JCOG1013) が計画されている。近年，分子標的薬剤や個別化治療が注目され，HER2陽性の進行胃癌に対する化学療法においてtrastuzumab併用による予後の改善が示された。この結果，胃癌の領域でも個別化治療の幕が開けた。今後，新たなバイオマーカーの研究が進み，個別化治療に関する新たな治療戦略が開発されることが期待される。

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Recent progress and future perspective of chemotherapy for advanced gastric cancer

Katsuhiko Higuchi, Wasaburo Koizumi

Department of Gastroenterology, Kitasato University School of Medicine

Gastric cancer is the second leading cause of cancer death behind lung cancer in Japan. Many randomized controlled trials of chemotherapies have been conducted, and the clinical outcomes of patients with advanced gastric cancer (AGC) have been improved. In Japan, the standard regimen for AGC is the combination of S-1 and cisplatin. Recently, new drug development has been focusing on molecular target agents, and personalized therapy for advanced gastric cancer has just started. In patients with HER-2 positive AGC, trastuzumab showed the survival benefit in combination with chemotherapy. Furthermore, a lot of information about the heterogeneity and the biological backgrounds of AGC has been accumulated. New strategies for the personalized therapy should be developed in the future.

Key words: gastric cancer, chemotherapy, molecular target agent, personalized therapy

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ORIGINAL ARTICLE

Efficacy of trastuzumab in Japanese patients with HER2-positive advanced gastric or gastroesophageal junction cancer: a subgroup analysis of the Trastuzumab for Gastric Cancer (ToGA) study

Akira Sawaki · Yasuo Ohashi · Yasushi Omuro · Taroh Satoh · Yasuo Hamamoto · Narikazu Boku · Yoshinori Miyata · Hiroya Takiuchi · Kensei Yamaguchi · Yasutsuna Sasaki · Tomohiro Nishina · Atsushi Satoh · Eishi Baba · Takao Tamura · Takashi Abe · Kiyohiko Hatake · Atsushi Ohtsu

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Abstract
Background The Trastuzumab for Gastric Cancer (ToGA) study is the first international trial to include Japanese patients with human epidermal growth factor 2 (HER2) positive advanced/metastatic gastric or gastroesophageal junction cancer. ToGA showed that trastuzumab plus chemotherapy (capecitabine/cisplatin or 5-fluorouracil/cisplatin) improved overall survival in the overall population (hazard ratio 0.74). Regional differences in outcome in favor of Japanese populations were observed in other studies; therefore, subgroup analyses of ToGA may contribute to the evaluation of the potential benefits of this regimen in Japanese patients.
Methods We performed subgroup analyses on 101 Japanese patients enrolled into ToGA (trastuzumab plus chemotherapy, $n = 51$; chemotherapy, $n = 50$).
Results Median overall survival in the Japanese subgroup was 15.9 months (95% confidence interval 12–25) for trastuzumab plus chemotherapy and 17.7 months (95% confidence interval 12–24) for chemotherapy (hazard ratio 1.00; 95% confidence interval 0.59–1.69). After adjusting

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A. Sawaki
Department of Gastroenterology, Aichi Cancer Center Hospital, Aichi, Japan

A. Sawaki (✉)
Division of Oncology, Nagoya Daini Red Cross Hospital, 2-9 Myoukenchou Shouwa-ku, Nagoya 466-8650, Japan
e-mail: sawaki@jk2.so-net.ne.jp

Y. Ohashi
Department of Biostatistics, Public Health Research Foundation, Tokyo, Japan

Y. Omuro
Department of Chemotherapy, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

T. Satoh
Department of Medical Oncology, Kinki University Faculty of Medicine, Osaka, Japan

Y. Hamamoto
Department of Medical Oncology, Tochigi Cancer Center, Tochigi, Japan

N. Boku
Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan

Y. Miyata
Department of Gastroenterology, Saku Central Hospital, Nagano, Japan

H. Takiuchi
Second Department of Internal Medicine, Osaka Medical College, Osaka, Japan

K. Yamaguchi
Division of Gastroenterology, Saitama Cancer Center, Saitama, Japan

Y. Sasaki
Department of Medical Oncology, Saitama International Medical Center–Comprehensive Cancer Center, Saitama Medical University, Saitama, Japan

T. Nishina
Department of Gastroenterology, National Hospital Organization Shikoku Cancer Center, Ehime, Japan

A. Satoh
Department of Internal Medicine, Toyosu Hospital, Showa University School of Medicine, Tokyo, Japan

E. Baba
Department of Hematology and Oncology, Kyushu University Hospital, Fukuoka, Japan

for prespecified covariates, the estimated hazard ratio for overall survival was 0.68 (95% confidence interval 0.36–1.27). Further post hoc and exploratory examinations supported the robustness of the adjusted hazard ratios.
Conclusions After adjusting for imbalanced patient backgrounds between arms, overall survival of Japanese patients with human epidermal growth factor 2 positive advanced/metastatic gastric or gastroesophageal junction cancer who received trastuzumab plus chemotherapy was improved compared with patients who received chemotherapy alone.

Keywords Trastuzumab · Drug therapy · Stomach neoplasms · Randomized controlled trial

Background

Approximately 110,000 people in Japan develop gastric cancer each year [1], with 65,000 estimated deaths (which is second only to lung cancer among cancer-related deaths [1]). For advanced disease, the oral fluoropyrimidine S-1, in combination with cisplatin, has become the standard treatment for gastric cancer in Japan, based on the results of the SPIRITS trial [2]. However, the prognosis still remains poor, and therefore new therapies such as molecular-targeted drugs are needed. Trastuzumab is a recombinant monoclonal antibody that targets human epidermal growth factor receptor 2 (HER2). Trastuzumab derives its anticancer effects from inducing antibody-dependent cytotoxicity, inhibiting HER2-mediated signaling, and preventing cleavage of the extracellular domain of HER2 [3].

Trastuzumab has been approved for use in HER2-positive metastatic breast cancer and as a postoperative adjuvant therapy for HER2-positive breast cancer, and is now the standard of care worldwide for these indications, including in Japan. The Trastuzumab for Gastric Cancer (ToGA) study was the first international randomized controlled phase III trial to include Japanese patients with HER2-positive advanced/metastatic gastric or gastroesophageal junction (GEJ) cancer. The percentage of patients with HER2-positive gastric cancer, as assessed by immunohistochemistry (IHC; 3+ on a scale of 0 to 3+) or fluorescence in situ hybridization (FISH; *HER2*:CEP17 ratio ≥2.0) was 22.1% in the overall ToGA population. The proportion of patients with HER2-positive disease was similar for Europe (23.6%), Asia (23.5%), and Japan (27.6%) [4], and similar to that seen in patients with breast cancer in other trial populations (25–30%) [5]. ToGA showed that patients who received combination treatment with trastuzumab and chemotherapy [capecitabine plus cisplatin (XP) or fluorouracil plus cisplatin (FP)] had significantly improved survival compared with those who received chemotherapy alone: the median overall survival (OS) in the intent-to-treat (ITT) population was 13.8 months in the trastuzumab plus chemotherapy arm and 11.1 months in the chemotherapy-only arm [hazard ratio (HR) 0.74, 95% confidence interval (CI) 0.60–0.91; $P = 0.0046$] [6].

There were substantial differences in OS reported from recent phase III trials of chemotherapy for gastric cancer, and these are especially evident between Japan and other countries. Recent trials in Japan have demonstrated that combination therapy resulted in longer survival than was seen in studies outside of Japan, with a median survival exceeding 1 year [7, 8], as compared with around 10 months in Western trials [9, 10]. There are considered to be two reasons for the longer survival observed in Japanese trials. Firstly, up to 70% of Japanese patients receive subsequent chemotherapy following failure of first-line therapy [11–13]. Secondary, there may be differences in the eligibility criteria and baseline patient characteristics between the Japanese and non-Japanese trials; the studies in Japan included patients with and without measurable metastatic disease, whereas non-Japanese trials usually included patients with measurable metastatic disease only [11]. Since the primary endpoint of the ToGA study was OS, there is a possibility that the impact of trastuzumab on survival might be reduced in Japanese patients due to inherently longer survival in this population. To evaluate the efficacy of trastuzumab in combination with chemotherapy specifically in the Japanese population of ToGA, we conducted preplanned and post hoc subgroup analyses.

Patients and methods

The details of the ToGA trial design and methods have been reported elsewhere [6].

Japanese patient subgroup

To evaluate the efficacy and safety of the combination treatment (trastuzumab plus XP) in the Japanese population

T. Tamura
Division of Diabetes, Digestive, and Kidney Diseases, Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine, Hyogo, Japan

T. Abe
Internal Medicine, Yamagata Prefectural Central Hospital, Yamagata, Japan

K. Hatake
Medical Oncology/Hematology, JFCR Cancer Institute Ariake Hospital, Tokyo, Japan

A. Ohtsu
Research Center for Innovative Oncology, National Cancer Center Hospital East, Chiba, Japan

of the ToGA study, we performed subgroup analyses using data from patients who were enrolled from institutions in Japan.

Preplanned sample size for Japanese patients

In the ToGA study, the HR for OS was expected to be 0.77, the expected number of events was 460, and the target sample size was set at 584 patients [6]. Before starting the ToGA study, we set the sample size of Japanese patients to allow us to evaluate similarities between the overall ToGA results and our subgroup analysis in an exploratory manner. Assuming a 70% probability that the HR for OS in the Japanese subgroup would be less than 0.88 (the midpoint between 0.77 and 1.00), the expected number of events was 70. To reach this expected number of events within the study period, the minimum sample size was determined to be 89 patients to allow us to conduct four analyses: preplanned (unadjusted and adjusted), post hoc, and exploratory analyses of the HR.

Unadjusted analyses

We calculated the unadjusted OS and progression-free survival (PFS) of the Japanese sub-group using the same methods as those used for the overall ToGA study [6]. Objective response rate of the Japanese sub-group was analysed with a χ^2 test in patients with measurable disease ($n = 45$ in the trastuzumab plus XP arm and 41 in the XP arm).

Preplanned analyses

Prior to carrying out the Japanese subgroup analysis, we predicted an imbalance in the baseline patient characteristics. Therefore, we planned to calculate an adjusted HR and 95% CI in the Japanese subgroup using a multivariate Cox regression analysis with 15 factors: extent of disease, primary tumor site, measurability of disease, Eastern Cooperative Oncology Group Performance Status (ECOG PS), chemotherapy regimen (stratification factors), sex, age, number of lesions, number of metastatic sites, type of gastric cancer, visceral metastasis, prior gastrectomy, prior chemotherapy, HER2 status, and region of origin (other prespecified covariates). All factors were prespecified in the ToGA study protocol. Each covariate was also evaluated using a univariate Cox regression analysis.

Post hoc analyses

During the preplanned multivariate Cox regression analysis, we excluded patients for whom HER2 status was reported as IHC 3+/FISH unknown (no result). In addition, estimates of effects were extremely unstable for covariates that contained a category which included only one patient. Therefore, to target all of the enrolled patients and ensure the stability of the model, a post hoc analysis was conducted using a multivariate Cox analysis. Among covariates, HER2 status was divided into two categories: high expression (IHC 2+ and FISH-positive or IHC 3+) and low expression (IHC0 and FISH-positive or IHC 1+ and FISH-positive). Covariates that contained a category with only one patient (extent of disease and previous chemotherapy) were excluded from the model to ensure its stability.

Exploratory analyses to evaluate deviation of patient prognosis

To identify factors that affect prognosis specifically in the Japanese subgroup, and to confirm the robustness of our preplanned and post hoc analyses, an exploratory multivariate Cox regression analysis on the HR for OS with various combinations of covariates was carried out. We created a series of models that included the treatment group as a base covariate with 3–6 other covariates, and selected the top four models ranked by value following a chi-square test. The procedure was repeated for the models with three, four, five, and six covariates, and a total of 16 models were selected. From the well-fitting model that was obtained, we compared the HR for OS with the results of preplanned and post hoc analyses. To ensure that HER2 status was not a confounding variable, we carried out a multivariate Cox regression analysis with HER2 expression (high or low) as the stratification factor, and determined the HR for OS in which selected covariates were included in the model.

Furthermore, scoring of the prognosis of each patient in both study arms using the Cox regression model and estimation of the risk for each patient were carried out with the selected covariates. The risk was shown by the estimated value of logarithm HR for each patient. To eliminate the influence of treatment on the mortality risk, we set the treatment group as the stratification factor and produced a histogram plot according to the distribution of patient risk to evaluate potential bias between the treatment arms.

Safety

Adverse events and serious adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 and the International Conference on Harmonization guidelines, respectively.

Results

Patients

Between September 2005 and December 2008, 594 patients were enrolled in the primary ToGA study at 122

Table 1 HER2 testing results in the Japanese population of ToGA

FISH result	IHC score				
	IHC 0	IHC 1+	IHC 2+	IHC 3+	Total
FISH-positive, *n*	14	19	36	37	106
FISH-negative, *n*	155	57	14	1	227
NE, *n*	48	12	8	8	83
Total, *n*	217	88	58	46	409

FISH fluorescence in situ hybridization, *HER2* human epidermal growth factor receptor 2, *IHC* immunohistochemistry, *NE* not evaluable

centers in 24 countries, of whom 584 were included in the primary analysis. Four hundred twenty-one tumor samples were provided for HER2 testing from 16 centers in Japan. Twelve samples were not evaluated due to a lack of tumor tissue in the sample ($n = 7$), shipment failure ($n = 4$), or disease progression before shipment ($n = 1$). Of the 409 samples successfully screened, 115 (28.1%) were scored as HER2-positive (IHC 3+ or FISH-positive; Table 1) and 102 patients were registered into the study. After excluding one patient who did not receive the study drug, 101 Japanese patients (trastuzumab plus chemotherapy, $n = 51$; chemotherapy alone, $n = 50$) were included in this subgroup analysis. All patients received capecitabine as the chemotherapy partner of cisplatin.

Table 2 shows the baseline characteristics of the Japanese patients included in this subgroup analysis ($n = 101$) and the non-Japanese patients ($n = 483$). There is similarity in the baseline characteristics of patients from other countries between the study arms. On the other hand, number of metastatic sites, histologic type, and prior gastrectomy were imbalanced by approximately 10% between the study arms in the Japanese subgroup, and were considered to be prognostic factors. Median follow-up times were 18.6 months [interquartile range (IQR) 11–25] in the trastuzumab plus XP arm and 17.1 months (IQR 1–49) in the XP arm. The median number of cycles of trastuzumab therapy was eight (range 1–24). Forty-one patients in the trastuzumab plus XP arm (80.4%) and 41 patients in the XP arm (82.0%) received second-line treatment (at least one chemotherapy treatment after disease progression despite the study treatments).

Efficacy

Unadjusted analyses

Twenty-eight patients (54.9%) in the trastuzumab plus XP arm and 27 patients (54.0%) in the XP arm had died by the data cutoff point. As shown in Table 3, unadjusted median OS was 15.9 months (95% CI 12–25 months) in the trastuzumab plus XP arm and 17.7 months (95% CI 12–24 months) in the XP arm (HR 1.00, 95% CI 0.59–1.69). The number of PFS events (defined as disease progression or death) was 43 (84.3%) in the trastuzumab plus XP arm and 40 (80.0%) in the XP arm. Unadjusted median PFS was 6.2 months (95% CI 5–7 months) in the trastuzumab plus XP arm and 5.6 months (95% CI 5–7 months) in the XP arm (HR 0.92, 95% CI 0.60–1.43). The objective response rate was 64.4% (95% CI 48.8–78.1%) in the trastuzumab plus XP arm and 58.5% (95% CI 42.1–73.7%) in the XP arm.

Preplanned analyses

In the multivariate analysis, the HR for OS, adjusted by the 15 prespecified covariates above, was 0.68 (95% CI 0.36–1.27, $P = 0.2251$, Table 4). The adjusted HR for PFS was 0.66 (95% CI 0.40–1.09%), which was slightly improved compared with the results for the overall population. Among the covariates in the preplanned analysis, the univariate analysis showed that prior gastrectomy was the covariate most strongly associated with longer OS (HR 0.39, 95% CI 0.16–0.91). There were more patients with prior gastrectomy in the XP arm (26%) than in the trastuzumab arm (16%). After adjusting for gastrectomy only, the HR for OS between the treatment arms was 0.85 (95% CI 0.49–1.45).

Post hoc analyses

For the post hoc exploratory multivariate Cox regression analysis, the adjusted HRs for OS and PFS were 0.82 (95% CI 0.45–1.50) and 0.81 (95% CI 0.50–1.30), respectively (Fig. 1).

Exploratory analyses to evaluate deviation of patient prognosis

We evaluated the HR for OS with different combinations of covariates in the model. In the well-fitting models with high chi-square values, the HRs using three, four, five, and six covariates ranged between 0.79 (95% CI 0.49–1.38) and 0.89 (95% CI 0.52–1.54), 0.77 (95% CI 0.44–1.33) and 0.88 (95% CI 0.51–1.53), 0.68 (95% CI 0.39–1.20) and 0.80 (95% CI 0.45–1.42), and 0.68 (95% CI 0.38–1.20) and 0.76 (95% CI 0.44–1.33), respectively. In choosing the well-fitting models, the covariates sex, HER2 status, type of gastric cancer, prior gastrectomy, prior chemotherapy, and number of lesions tended to be chosen. The sets of covariates were similar to those used as prespecified covariates (15 factors). A similar analysis was carried out

Table 2 Baseline patient characteristics of the Japanese population and the non-Japanese population of ToGA

Characteristic	Japanese		Non-Japanese	
	Trastuzumab plus XP ($n = 51$)	XP/FP ($n = 50$)	Trastuzumab plus XP ($n = 243$)	XP/FP ($n = 240$)
Sex				
Male, *n*	40 (78.4%)	40 (80.0%)	186 (76.5%)	178 (74.2%)
Median age, years (range)	63.0 (29–76)	63.5 (45–81)	60.0 (23–83)	59.0 (21–82)
Extent of disease				
Locally advanced, *n*	0 (0.0%)	1 (2.0%)	10 (4.1%)	9 (3.8%)
Metastatic, *n*	51 (100.0%)	49 (98.0%)	233 (95.9%)	231 (96.3%)
Primary tumor site				
Stomach, *n*	49 (96.1%)	44 (88.0%)	187 (77.0%)	198 (82.5%)
Gastroesophageal junction, *n*	2 (3.9%)	6 (12.0%)	56 (23.0%)	42 (17.5%)
Measurability of disease				
Measurable, *n*	45 (88.2%)	41 (82.0%)	224 (92.2%)	216 (90.0%)
Nonmeasurable, *n*	6 (11.8%)	9 (18.0%)	19 (7.8%)	24 (10%)
ECOG performance status				
0–1, *n*	51 (100.0%)	50 (100.0%)	213 (87.7%)	213 (88.7%)
2, *n*	0 (0.0%)	0 (0.0%)	30 (12.3%)	27 (11.3%)
Chemotherapy regimen				
XP, *n*	51 (100%)	50 (100%)	205 (84.4%)	205 (85.4%)
FP, *n*	0 (0.0%)	0 (0.0%)	38 (15.6%)	35 (14.6%)
Number of lesions			($n = 242$)	
1–4, *n*	16 (31.4%)	18 (36.0%)	112 (46.3%)	98 (40.8%)
>4, *n*	35 (68.6%)	32 (64.0%)	130 (53.7%)	142 (59.2%)
Median value (range)	6 (1–15)	6 (1–15)	5 (1–20)	5 (1–16)
Number of metastatic sites			($n = 242$)	
1–2, *n*	28 (54.9%)	32 (64.0%)	124 (51.2%)	114 (47.5%)
>2, *n*	23 (45.1%)	18 (36.0%)	118 (48.8%)	126 (52.5%)
Median value (range)	2 (1–5)	2 (1–5)	2 (1–7)	3 (1–8)
Type of gastric cancer (central review)[a]			($n = 242$)	($n = 237$)
Intestinal type, *n*	37 (72.5%)	42 (84.0%)	188 (77.7%)	171 (72.2%)
Diffuse type, *n*	5 (9.8%)	4 (8.0%)	21 (8.7%)	21 (8.9%)
Mixed type, *n*	9 (17.6%)	4 (8.0%)	33 (13.6%)	45 (19.0%)
Visceral metastasis (liver or lung)				
Yes, *n*	35 (68.6%)	33 (66.0%)	134 (55.1%)	139 (57.9%)
No, *n*	16 (31.4%)	17 (34.0%)	109 (44.9%)	101 (42.1%)
History of treatment for gastric cancer				
Prior gastrectomy, *n*	8 (15.7%)	13 (26.0%)	62 (25.5%)	49 (20.4%)
Prior chemotherapy, *n*	1 (2.0%)	0 (0.0%)	26 (10.7%)	12 (5.0%)
HER2 status				
IHC 0/FISH-positive, *n*	3 (5.9%)	9 (18.0%)	20 (8.2%)	29 (12.2%)
IHC 1+/FISH-positive, *n*	10 (19.6%)	7 (14.0%)	28 (11.5%)	25 (10.4%)
IHC 2+/FISH-positive, *n*	18 (35.3%)	13 (26.0%)	62 (25.5%)	66 (27.5%)
IHC 3+/FISH-positive, *n*	16 (31.4%)	17 (34.0%)	115 (47.3%)	108 (45.0%)
IHC 3+/FISH-negative, *n*	1 (2.0%)	0 (0.0%)	8 (3.3%)	6 (2.5%)
IHC unknown/FISH-positive, *n*	0 (0.0%)	0 (0.0%)	5 (2.1%)	2 (0.8%)
IHC 3+/FISH unknown, *n*	3 (5.9%)	4 (8.0%)	5 (2.1%)	4 (1.7%)
Region of origin				
Japanese, *n*	51 (100%)	50 (100%)	0 (0.0%)	0 (0.0%)
Non-Japanese, *n*	0 (0.0%)	0 (0.0%)	243 (100%)	240 (100%)

ECOG Eastern Cooperative Oncology Group, *FISH* fluorescence in situ hybridization, *HER2* human epidermal growth factor receptor 2, *IHC* immunohistochemistry, *XP* capecitabine plus cisplatin

[a] Type of gastric cancer was described by the Lauren Classification

using HER2 expression (high or low) as the stratification factor. The HR was approximately 0.7, and the HRs using three, four, five, and six covariates were between 0.67 (95% CI 0.38–1.18) and 0.79 (95% CI 0.46–1.39), 0.70 (95% CI 0.40–1.24) and 0.82 (95% CI 0.47–1.42), 0.68 (95% CI 0.39–1.22) and 0.76 (95% CI 0.43–1.34), and 0.67 (95% CI 0.37–1.22) and 0.78 (95% CI 0.44–1.36), respectively. Influential covariates chosen in the well-fitting models included sex, prior gastrectomy, and number of lesions. Table 5 shows the covariate combinations that resulted in a good fit based on these analyses. Figure 2 shows the distribution of patient risk with these three models. The risk distribution is broad in each arm; however, the XP arm shows a somewhat greater distribution toward the left, indicating that this arm included a greater number of patients with better prognosis.

Table 3 Overall survival in the Japanese population of ToGA (unadjusted Cox regression analysis)

	Trastuzumab plus XP ($n = 51$)	XP ($n = 50$)
Number of events (%)	28 (54.9)	27 (54)
Median OS, months (95% CI)	15.9 (12–25)	17.7 (12–24)
Survival rate (%)		
6 months	92	92
12 months	68	64
18 months	48	49
24 months	41	35
Hazard ratio (95% CI)	1.00 (0.59–1.69)	

CI confidence interval, *OS* overall survival, *XP* capecitabine plus cisplatin

Safety

Table 6 shows the adverse events in the Japanese population of ToGA, and indicates that all patients experienced at least one adverse event in each arm. Grade 3/4 adverse events occurred in 43 patients (84%) in the trastuzumab

Table 4 Preplanned multivariate Cox regression analysis of overall survival by extent of disease, primary tumor site, measurability of disease, ECOG status, chemotherapy regimen, and other prespecified covariates: sex, age, number of lesions, number of metastatic sites, type of gastric cancer, visceral metastasis, prior gastrectomy, prior chemotherapy, HER2 status, and region of origin

	Hazard ratio (95% CI)		*P* value
Trastuzumab plus XP versus XP	0.68	(0.36–1.27)	0.2251
Sex (male vs. female)	0.16	(0.07–0.41)	<0.0001
Age (<60 vs. ≥60)	1.07	(0.54–2.13)	0.8382
Extent of disease (locally advanced vs. metastatic)	0.00	(0.00–.)	0.9902
Primary tumor site (stomach vs. gastroesophageal junction)	0.68	(0.25–1.87)	0.4559
Measurability of disease (measurable vs. nonmeasurable)	0.95	(0.29–3.05)	0.9268
ECOG performance status	–	–	–
Chemotherapy regimen	–	–	–
Number of lesions (1–4 vs. >4)	0.49	(0.22–1.09)	0.0818
Number of metastatic sites (1–2 vs. >2)	0.79	(0.41–1.50)	0.4695
Type of gastric cancer			
Diffuse type versus intestinal type	3.24	(1.08–9.70)	0.0356
Mixed type versus intestinal type	0.91	(0.30–2.71)	0.8644
Visceral metastasis (yes vs. no)	1.15	(0.48–2.74)	0.7510
Prior gastrectomy (yes vs. no)	0.22	(0.06–0.75)	0.0159
Prior chemotherapy (yes vs. no)	27.72	(1.11–694.38)	0.0432
HER2 status			
IHC 0/FISH-positive versus IHC 3+/FISH-positive	5.31	(1.29–21.86)	0.0208
IHC 1+/FISH-positive versus IHC 3+/FISH-positive	4.87	(1.73–13.70)	0.0027
IHC 2+/FISH-positive versus IHC 3+/FISH-positive	1.53	(0.73–3.18)	0.2578
IHC 3+/FISH-negative versus IHC 3+/FISH-positive	25.66	(1.72–382.49)	0.0186
Region of origin	–	–	–

Among 15 prespecified factors, chemotherapy regimen, performance status, and region of origin were not calculated in this table because all Japanese patients received capecitabine as the chemotherapy partner of cisplatin, had Karnofsky performance status of 0–1, and were from Asia (Japan)

CI confidence interval, *ECOG* Eastern Cooperative Oncology Group, *FISH* fluorescence in situ hybridization, *HER2* human epidermal growth factor receptor 2, *IHC* immunohistochemistry, *XP* capecitabine plus cisplatin

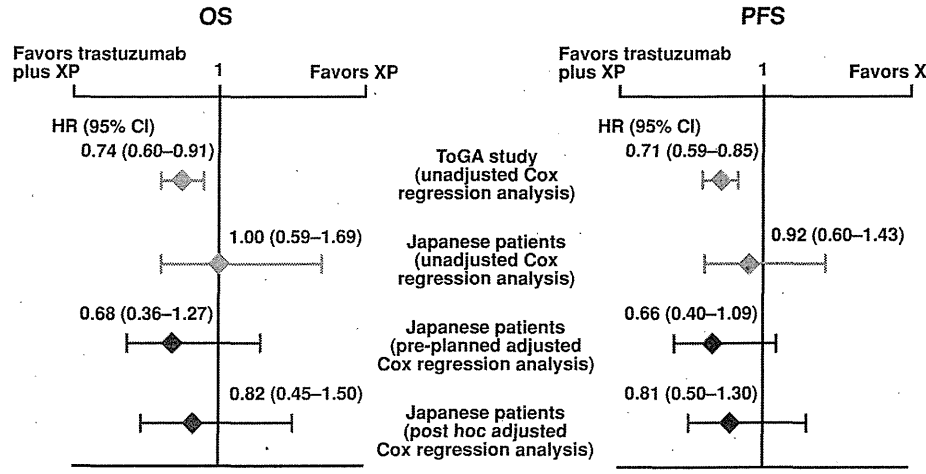

Fig. 1 Unadjusted and adjusted hazard ratios for overall and progression-free survival. *CI* confidence interval, *HR* hazard ratio, *OS* overall survival, *PFS* progression-free survival, *XP* capecitabine plus cisplatin

Table 5 Covariates included in the model

Number of covariates	Covariates included in the model
4	HER2 expression (low/high), sex (male/female), prior gastrectomy (yes/no), number of lesions (1–4/>4)
5	HER2 expression (low/high), sex (male/female), prior gastrectomy (yes/no), number of lesions (1–4/>4), type of gastric cancer (diffuse/intestinal)
6	HER2 expression (low/high), sex (male/female), prior gastrectomy (yes/no), number of lesions (1–4/>4), type of gastric cancer (diffuse/intestinal), number of metastatic sites (1–2/>2)

HER2 human epidermal growth factor receptor 2

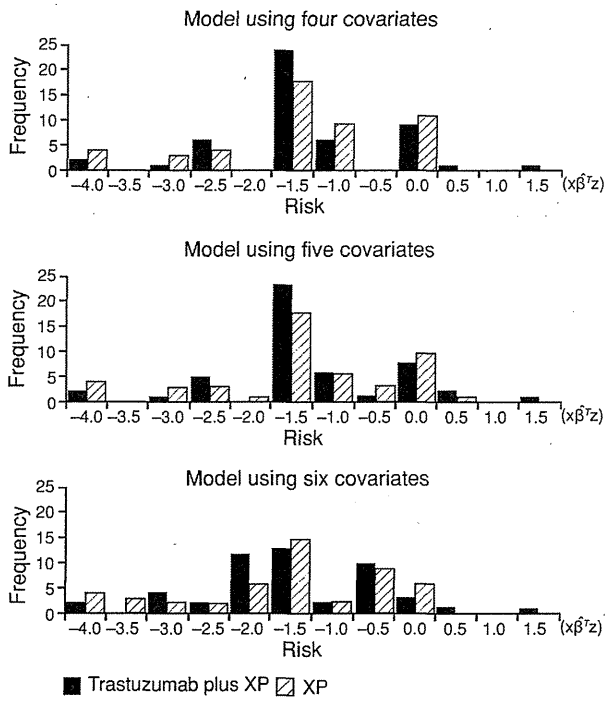

Fig. 2 Distribution of estimated values by linear predictor. *XP* capecitabine plus cisplatin. The ordinate is the number of patients and the abscissa is the risk score (estimated hazard number for each patient). The risk of mortality increases as the plot moves to the right

plus XP arm and 36 patients (72%) in the XP arm. Treatment was discontinued due to adverse events for one patient (2%) in the trastuzumab plus XP arm and four patients (8%) in the XP arm. Deaths due to adverse events occurred in two patients in the trastuzumab plus XP arm: one due to cardiac failure and unstable angina and the other due to gastrointestinal perforation. The case of cardiac failure and unstable angina was attributed to an adverse event likely related to trastuzumab.

Discussion

In the original ToGA study, patients with HER2-positive advanced gastric or GEJ cancer who received the combination treatment of trastuzumab plus XP/FP had significantly longer OS and PFS than patients who received XP/FP alone [6]. No differences in OS or PFS were detected between the two treatment arms in this subgroup analysis of Japanese patients when unadjusted data were analyzed. However, in preplanned and post hoc analyses, the HRs were 0.68 and 0.82 for OS and 0.66 and 0.82 for PFS, respectively, after adjusting for baseline characteristics. These values were similar to the overall ToGA study results. Taken together, these results strongly suggest that

Table 6 Adverse events in ≥10% of Japanese patients in ToGA

	Trastuzumab plus XP (n = 51)		XP (n = 50)	
	All grade n (%)	Grade ≥3 n (%)	All grade n (%)	Grade ≥3 n (%)
Total	51 (100)	43 (84)	50 (100)	36 (72)
Gastrointestinal disorders				
Nausea	44 (86)	7 (14)	44 (88)	7 (14)
Vomiting	33 (65)	1 (2)	28 (56)	2 (4)
Constipation	24 (47)	1 (2)	24 (48)	–
Diarrhoea	23 (45)	4 (8)	24 (48)	2 (4)
Stomatitis	29 (57)	–	16 (32)	1 (2)
Blood and lymphatic system disorders				
Neutropenia	30 (59)	18 (35)	34 (68)	20 (40)
Thrombocytopenia	11 (22)	1 (2)	8 (16)	3 (6)
Anemia	15 (29)	13 (25)	11 (22)	8 (16)
Febrile neutropenia	5 (10)	5 (10)	3 (6)	3 (6)
Skin and subcutaneous tissue disorders				
Palmar–plantar erythrodysaesthesia syndrome	21 (41)	–	23 (46)	1 (2)
Alopecia	12 (24)	–	9 (18)	–
Skin hyperpigmentation	6 (12)	–	5 (10)	–
Rash	10 (20)	–	5 (10)	–
Pigmentation disorder	10 (20)	–	7 (14)	–
Nail disorder	5 (10)	–	5 (10)	–
Metabolism and nutrition disorders				
Anorexia	43 (84)	12 (24)	46 (92)	10 (20)
Dehydration	3 (6)	1 (2)	6 (12)	1 (2)
General disorders and administration site conditions				
Fatigue	31 (61)	4 (8)	26 (52)	4 (8)
Pyrexia	19 (37)	1 (2)	12 (24)	–
Chill	7 (14)	–	0 (0)	–
Edema	19 (37)	–	23 (46)	–
Nervous system disorders				
Peripheral neuropathy	16 (31)	1 (2)	10 (20)	–
Dysgeusia	13 (25)	–	8 (16)	–
Peripheral sensory neuropathy	2 (4)	–	11 (22)	–
Dizziness	5 (10)	1 (2)	5 (10)	–
Respiratory, thoracic, and mediastinal disorders				
Hiccups	21 (41)	–	16 (32)	–
Epistaxis	5 (10)	–	3 (6)	–
Renal and urinary disorders				
Renal impairment	32 (63)	2 (4)	27 (54)	–
Vascular disorders				
Hypertension	4 (8)	1 (2)	3 (6)	–
Investigations				
Weight decreased	27 (53)	2 (4)	13 (26)	1 (2)
Weight increased	10 (20)	1 (2)	9 (18)	–
Psychiatric disorders				
Insomnia	11 (22)	–	8 (16)	–
Infections and infestations				
Nasopharyngitis	18 (35)	–	6 (12)	–
Musculoskeletal and connective tissue disorders				
Back pain	5 (10)	–	1 (2)	–

XP capecitabine plus cisplatin

the same benefit of adding trastuzumab to chemotherapy was obtained in the Japanese patient subgroup as in the overall population.

In our subgroup analysis, the change in HR pre- and post-adjustment may have been due to an uneven distribution of prognostic factors between the two treatment arms. The XP arm included more patients with factors generally considered to be associated with a good prognosis (history of gastrectomy [14, 15], intestinal type cancer [16–19], and metastasis in fewer than two organs [19]). In the overall ToGA study and in the Japanese subgroup, gastric resection was shown to be the most influential factor affecting prognosis, as assessed by univariate Cox regression analyses (HRs of gastrectomy were 0.54 and 0.39, respectively). In the Japanese subgroup, the number of patients who had undergone gastric resection in the XP arm ($n = 13$, 26.0%) was approximately 10% higher than that of the trastuzumab plus XP arm ($n = 8$, 15.7%).

When multiple factors influence prognosis, different combinations of factors could affect the HR between two treatment groups. Therefore, to confirm that the HR is robust, it is necessary to analyze different combinations of factors. In this regard, we found that the HRs for OS were approximately 0.7 for all combinations of factors, thus supporting the robustness of our results.

Median OS in the XP/FP alone arm was 11.1 months (95% CI 10–13) in the overall ToGA population [6], but was approximately 6.5 months longer in the Japanese subgroup (XP arm: 17.7 months). These findings are consistent with results of recent trials reporting longer survival for patients with gastric cancer in Japan than for patients in Europe and the USA. One possible reason for this difference is that more Japanese patients receive second-line or later treatment after the failure of first-line treatment [11–13]. In the ToGA study, more than 80% of Japanese patients in both treatment arms underwent second-line or further treatment, which was considerably higher than the overall rates of second-line treatment in the overall ToGA population (42% of patients in the trastuzumab plus XP/FP arm and 45% in the XP/FP arm) [6]. In the present study of Japanese patients, the OS of patients who received XP only was similar to that reported in other recent Japanese trials [2, 7, 8]. Furthermore, after adjusting for imbalances between the baseline characteristics of treatment arms, we detected an additive effect of trastuzumab among Japanese patients, similar to that of the overall population. By further exploratory analyses, we confirmed that the HRs in favor of trastuzumab were consistently observed after adjusting for prognostic factors. These findings strongly suggest that the benefits of trastuzumab were of the same magnitude in Japanese patients as in the whole study population, although the absolute length of survival was longer in the Japanese subgroup. In conclusion, trastuzumab in combination with XP can be considered a new standard therapy for Japanese patients with HER2-positive advanced gastric or GEJ cancer.

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