Patients in whom curative resection was impossible underwent palliative operation. The postoperative treatment was left to the decision of each physician.

Biostatistical considerations

The 3 primary end points of the study were as follows; 1) tolerance to preoperative chemotherapy, 2) operative morbidity and mortality, and 3) objective response rate (ORR). Secondary end points were R0 resection rate, failure pattern, and disease-free and overall survival. One of the primary end points was ORR. The number of patients to be enrolled was calculated at 24, which was required given the assumption that the 95% confidence interval (CI) would be ±20%, assuming an expected response rate of 60%. Finally, we set the number as 30 patients in consideration of disqualified patients. The early stopping criterion of the trial was 3 treatment related deaths. Analogous samples were used to estimate the response rate, R0 resection rate, operative morbidity and mortality, and incidence of treatment related grade 3–4 toxicity. Overall survival (OS) of all patients was calculated from the day of registration in the trial. OS and disease-free survival (DFS) of the patients who underwent R0 resections were calculated from the day of surgery. Survival distributions were estimated using the Kaplan–Meier method.

Follow-up

Following completion of chemotherapy and surgery, patients were followed at 3- monthly intervals until year 3. Thereafter, 6-month follow-up visits were performed. CT scans and appropriate blood studies were performed on the occasion of each evaluation.

Results

Patient population

Between December 2000 and December 2007, 27 patients with initially unresectable local advanced gastric cancer were enrolled into the study from 9 institutions. As shown in Table 1, the male to female ratio was 20:7. The median age was 63 years. As for the histologic type, 15 cases were undifferentiated (including signet ring cell carcinoma) and 11 cases were differentiated type. One case was classified as mucinous carcinoma. There were 3 cStage IIIa (11.1%) preoperatively, 8 cStage IIIb (29.6%), and 16 cStage IV (59.3%).

Preoperative chemotherapy

The median number of preoperative chemotherapy regimens was 3 courses. Grade 3–4 toxicities associated with preoperative S-1/CDDP are described in Table 2. Hematologic toxicity (Grade 3/4) was 7.4% and non-hematologic toxicity (Grade 3/4) was 3.7%. Treatment was generally well tolerated and no chemotherapy-related deaths were observed. While there was no CR, there were 17 cases of PR and the response rate was 63.0% [95%CI: 42.4–80.6] (Table 2).

Table 1
Patient characteristics (n = 27).

		Number	%
Age, years	Median (range)	63	(48–75)
Gender	Male	20	74.1
	Female	7	25.9
Histology	Differentiated	11	40.7
	Undifferentiated	15	55.6
	Other	1	3.7
Pretreatment cStage	T2N2M0 (IIIA)	3	11.1
	T3N2M0 (IIIB)	7	25.9
	T4N1M0 (IIIB)	1	3.7
	T2N3M0 (IV)	5	18.5
	T3N3M0 (IV)	6	22.2
	T4N2M0 (IV)	3	11.1
	T4N3M0 (IV)	2	7.4

Operative outcome

All patients who were entered into this trial had initially unresectable tumors. Nine patients were diagnosed as being unresectable when chemotherapy was completed and did not undergo surgery. Eighteen patients (66.7%) underwent laparotomy (Table 3). Thirteen patients (48.1%) had R0 resections. Three patients (11.1%) underwent R1 surgery, because of positive results of peritoneal washing cytology. Two patients underwent simple laparotomy because of peritoneal metastases or unresectable local extension of metastatic lymph nodes. Postoperative complications are described in Table 3. The incidence of complications was 22.2%. One patient underwent operative intervention because of pancreatic leakage; however, there were no surgery-related deaths.

Table 2
Courses, responses and toxicities of preoperative chemotherapy.

				n	%
Courses	Median (range)			3	(1–9)
Response	CR			0	0.0
	PR			17	63.0
	SD			6	22.2
	PD			4	14.8
Toxicities		Grade1/2		Grade3/4	
		n	%	n	%
	Neutropenia	10	37.0	2	7.4
	Thrombocytopenia	3	11.1	1	3.7
	Hemoglobin	21	77.8	1	3.7
	Vomiting	7	25.9	1	3.7
	Nausea	13	48.1	1	3.7
	Diarrhea	4	14.8	1	3.7
	Anorexia	17	63.0	1	3.7
	Cerebral infarction	0	0	1	3.7
Treatment related death				0	0.0

Table 3
Operative outcome ($n = 27$).

		Number	%
No operation		9	33.3
Operation		18	66.7
	R0 resection	13	48.1
	R1 resection	3	11.1
	R2 resection	0	0
	Simple Laparotomy	2	22.2
Complications			
	None	14	77.8
	Pancreatic leak	3 (Grade 1: 2, Grade 4: 1)	16.7
	Lymphorrhea	1 (Grade 1)	5.6
	Anastomotic leak	0	0.0
Re-operation		1	5.6
Mortality		0	0.0

Seven of 9 patients who did not undergo surgery received 2nd-line chemotherapy (S-1: 3 patients, S-1/CPT-11: 2 patients, CPT-11/CDDP: 1 patient, Paclitaxel: 1 patient). Four of 5 patients who underwent R1-2 surgery received further chemotherapy (S-1/Paclitaxel: 2 patients, S-1: 1 patient, CPT-11/CDDP: 1 patient).

Overall survival of all patients

Only one patient was lost to follow-up at 8 months from the first day of preoperative chemotherapy, but all other patients were followed more than three years. The median overall survival time and the 3-year overall survival rate of all patients were 31.4 months and 31.0% [95%CI: 17.5–55.1], respectively.

DFS, OS, and first relapse site of patients who underwent R0 resection

Thirteen patients underwent R0 resection. The details of these patients are shown in Table 4. Twelve of these 13 patients (92.3%) achieved PR after preoperative chemotherapy. The median number of course of chemotherapy of these patients was 3 (2–5). Of these patients, only 2 patients (15.4%) underwent D2 plus para-aortic lymph node dissection (D3). Downstaging was observed in 11 patients (84.6%). Seven of 13 patients received postoperative adjuvant chemotherapy (S-1: 4 patients, S-1 plus CDDP: 1 patient, CPT-11: 1 patient, CPT-11/CDDP: 1 patient). To date, recurrence has been diagnosed in 10 patients. First relapse site of five of ten patients was para-aortic lymph nodes. The median disease-free survival time and the 3-year disease-free survival rate of the 13 patients were 17.4 months and 23.1% [95%CI: 8.6–62.3], respectively (Fig. 1A). The median overall survival time and the 3-year overall survival rate of the 13 patients were 50.1 months and 53.8% [95% CI: 32.6–89.1], respectively (Fig. 1B).

Discussion

The combination chemotherapy of S-1 plus cisplatin was chosen because it had achieved a high response rate of 74% (95%CI: 54.9–90.6) in previous phase I/II study of patients with metastatic gastric cancer. The incidences of severe (Grade 3/4) hematological and non-hematological toxicities were 15.8 and 26.3%, respectively.[7] A randomized controlled trial in Japan showed the superiority of S-1/cisplatin compared with S-1 monotherapy according to the response rate and survival for metastatic gastric cancer.[11] Therefore, S-1/cisplatin therapy is now the standard treatment for metastatic gastric cancer in Japan.

This multi-institutional phase II prospective trial of preoperative chemotherapy in initially unresectable locally advanced gastric cancer showed that preoperative chemotherapy using S-1/cisplatin was not only feasible but also achieved a high response rate. The overall response rate was 63.0% [95%CI: 42.4–80.6]. The incidence of grade 3/4 toxicities was less than 10% and treatment related

Table 4
Patients who underwent R0 resection.

No.	cStage	Course	Response	Gastrectomy	D	Combined resection	fStage	Nodes	First relapse
1	T3N2M0 (IIIB)	2	PR	Distal	D3	Liver, Gallbladder	T2N2M0 (IIIA)	4	None
2	T3N3M0 (IV)	3	PR	Total	D2	Spleen, Panc. (tail) Gallbladder	T2N2M0 (IIIA)	6	Brain
3	T3N2M0 (IIIB)	2	PR	Total	D2	Spleen	T2N2M0 (IIIA)	10	Lymph (para AO)
4	T3N2M0 (IIIB)	2	PR	Distal	D3	None	T2N2M0 (IIIA)	3	None
5	T3N2M0 (IIIB)	3	PR	Total	D1*	Liver	T2N0M0 (IB)	0	None
6	T2N2M0 (IIIA)	2	SD	Distal	D2	Panc. (head)	T4N3M0 (IV)	7	Peritoneum
7	T4N2M0 (IV)	3	PR	Total	D2	Spleen, Panc. (tail)	T3N2M0 (IIIB)	10	Lymph (para AO)
8	T2N3M0 (IV)	4	PR	Distal	D2	Gallbladder	T2N2M0 (IIIA)	1	Bone
9	T4N3M0 (IV)	3	PR	Distal	D2	None	T1N0M0 (IA)	0	Lung
10	T4N1M0 (IIIB)	3	PR	Total	D2	Spleen	T2N2M0 (IIIA)	4	Lymph (hepatic)
11	T2N3M0 (IV)	5	PR	Total	D1*	None	T2N3M0 (IV)	2	Lymph (para AO)
12	T2N2M0 (IIIA)	3	PR	Total	D1*	None	T2N0M0 (IB)	0	Lymph (para AO)
13	T3N2M0 (IIIB)	3	PR	Total	D1*	None	T2N2M0 (IIIA)	13	Lymph (para AO)

D1*: we performed almost D2 dissection, but it classified D1 dissection according to the Japanese classification of gastric carcinoma (2nd English edition), because of preserving spleen.

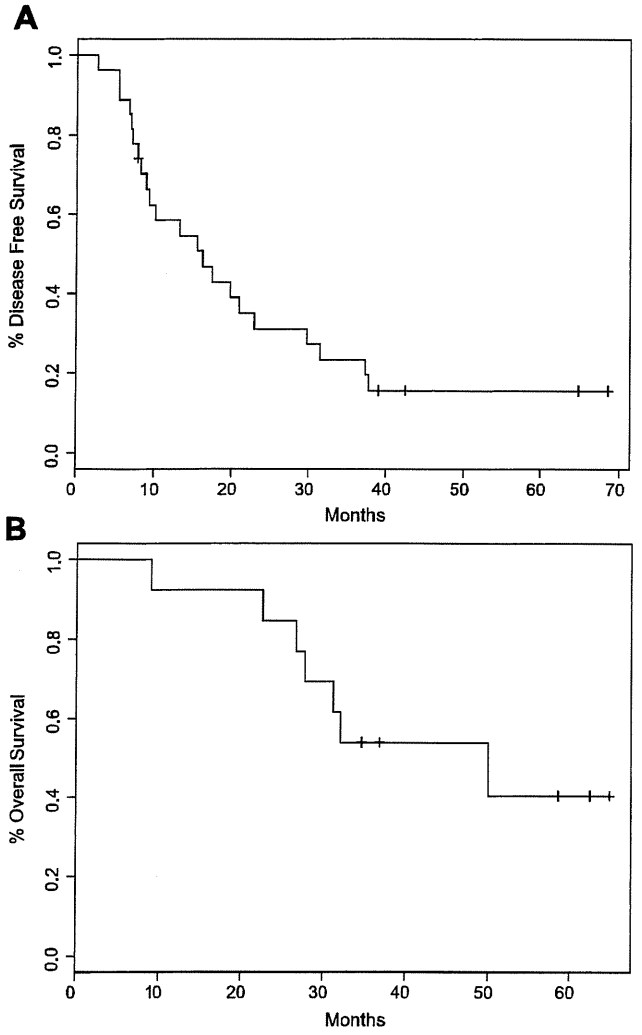

Figure 1. Disease-free and overall survival of the patients who underwent R0 surgery ($n = 13$).

mortality was 0.0%. Similar results were reported in other studies.[12,13] These results encourage the use of S-1/cisplatin combination chemotherapy as neoadjuvant treatment for patients who have resectable gastric cancer. Such trials are currently under way in Japan.[14,15]

The recently completed MAGIC trial constitutes a larger study regarding neoadjuvant chemotherapy in gastric cancer. In this study, 503 patients were randomized to three cycles of pre- and three cycles of postoperative epirubicin/cisplatin/5-FU (ECF) chemotherapy or surgery alone. Neoadjuvant chemotherapy was tolerable and was completed in 88% of patients. Significant downsizing (5.0 versus 3.1 cm median tumor size, $P < 0.001$), downstaging (54% versus 36% T1–T2 tumors, $P = 0.01$) and enhanced resectability (79% versus 69%, $P = 0.02$) were noted. Improved progression-free survival and survival were demonstrated, with an overall 5-year survival of 36% versus 23% for those undergoing surgery alone.[16] We should conduct phase III clinical trials of the neoadjuvant chemotherapy of S-1/cisplatin therapy for resectable gastric cancer.

In Japan, the ACTS-GC trail demonstrated a survival advantage of postoperative adjuvant chemotherapy after R0 resection. R0 patients were randomized to adjuvant chemotherapy using S-1 (529 patients) versus surgery alone (530 patients); improved survival (3-year overall survival rates of 80.1% versus 70.1%, $P = 0.003$) was noted.[17] Adjuvant chemotherapy, as reported by the ACTS-GC Group, is now considered a standard treatment for R0 patients. However, of the 283 patients who had stage III disease and received S-1 adjuvant chemotherapy, 73 patients died. The hazard ratio of the adjuvant chemotherapy group worsened with an increasingly advanced stage. These results suggest that S-1 monotherapy is insufficient for patients who have stage III or more. However, for patients who have initially unresectable gastric cancer like the patients enrolled in this trial, S-1/cisplatin chemotherapy is insufficient because of the high relapse rate of patients who underwent R0 resection.

For the patients immediately after gastrectomy, highly toxic chemotherapy is difficult because of overlaps between chemotherapy-induced gastrointestinal toxicity and digestive symptoms due to gastrectomy.[18] Therefore, further improvements in preoperative therapy will require development of more effective chemotherapeutic regimens. During the last decade, several new agents with promising activity against gastric cancer were identified. These include paclitaxel, docetaxel, irinotecan and trastuzumab. These agents are now undergoing phase II and III trials, as part of combination regimens.[19–22] If improved outcome is seen in metastatic disease, these agents will undergo extensive testing in the preoperative setting.

The absence of laparoscopic staging might have allowed inclusion of patients with positive peritoneal cytology or small peritoneal implants that could have disappeared with the chemotherapy; these patients have a worse prognosis, which could have impacted on the final results. Actually, there were 3 cases of positive cytology at exploration after chemotherapy. Laparoscopic staging should be mandatorily included in future similar projects.

An interesting point is that there were many para-aortic lymph node recurrences in the patients who underwent R0 resection. Among 13 patients who underwent curative resection, initial recurrence in 5 patients was in a para-aortic lymph node. These patients had not undergone para-aortic lymph node dissection. The prognostic improvement effect of the para-aortic lymph node dissection was refuted by two clinical trials.[23,24] In the JCOG 9501 trial, 523 patients with resectable gastric cancer were enrolled, and 263 were assigned to D2 group and 260 were assigned to D2 plus para-aortic nodal dissection. The 5-year overall survival rate was 69.2% for D2 lymphadenectomy group and 70.3% for the D2 lymphadenectomy plus para-aortic nodal dissection group; the hazard ratio for death was 1.03 (95%CI, 0.77 to 1.37; $P = 0.85$). There were also no significant differences in recurrence-free

survival and the pattern of recurrence between the two groups.[23] In the East Asian Surgical Oncology Group trial, 269 patients with resectable gastric cancer were enrolled, and 135 were assigned to the D2 group and 134 were assigned to the D2 plus para-aortic nodal dissection. The 5-year overall survival rates were 52.6% for the D2 lymphadenectomy group and 55.0% for the D2 lymphadenectomy plus para-aortic nodal dissection group. There was no significant difference in survival between the two groups ($P = 0.801$).[24] It was concluded that the D2 lymphadenectomy plus para-aortic nodal dissection did not improve prognosis regarding D2 lymph node dissection in the resectable gastric cancer.

However, in these trials, patients who had gross metastases to the para-aortic nodes were excluded. The incidence of metastases in the para-aortic nodes was lower than expected in 8.5% and 9.7%, respectively. The median number of metastatic nodes was only 2 nodes among the patients who underwent D2 plus para-aortic nodal dissection in the JCOG 9501. In the East Asian Surgical Oncology Group trial, the mean number of metastatic nodes was 5.9 in the para-aortic lymph node dissection group.

Recently, 15-year follow-up results of a randomized nationwide Dutch D1D2 trial were published. 711 patients underwent randomly assigned treatment with curative intent (380 in the D1 group and 331 in the D2 group). Overall 15-year survival was 21% for the D1 group and 29% for the D2 group. Gastric cancer-related death rate was significantly higher in the D1 group (48%, 182 patients) than that in the D2 group (37%, 123 patients). Local recurrence was 22% (82 patients) in the D1 group versus 12% (40 patients) in D2, and regional recurrence was 19% (73 patients) in D1 versus 13% (43 patients) in D2. After a median follow-up of 15 years, D2 lymphadenectomy was associated with lower locoregional recurrence and gastric cancer-related death rates than D1 surgery.[25] This difference was greater in the patients with lymph node metastases from 7 to 15.[26]

The observation period was shorter in the clinical trials of JCOG and East Asian Surgical Oncology Group than in the Dutch trail, and fewer mortality events occurred and also fewer metastases to lymph nodes. Therefore, para-aortic lymph node dissection might have better prognosis in patients with severe lymph node metastases like the patients enrolled in our trial.

In summary, preoperative S-1/cisplatin can be safely delivered to patients undergoing radical gastrectomy. The response rate was high, with no increase in operative morbidity and mortality compared with those upon surgery without preoperative chemotherapy.[27] Controlled trials of neoadjuvant chemotherapy using this regimen with the postoperative S-1 monotherapy for resectable gastric cancer are necessary. For initially unresectable locally advanced gastric cancer, the rate of recurrence was high, and the most common initial recurrent site was para-aortic lymph node. New trials, using a more effective regimen along with extended lymph node dissection are necessary.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgments

The authors thank the members of the OGSG data center and operations office. The authors are also indebted to Prof. J. Patrick Barron, Chairman of the Department of International Medical Communications of Tokyo Medical University, for his review of this manuscript.

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Gastric Cancer
DOI 10.1007/s10120-011-0118-1

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

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Received: 6 August 2011 / Accepted: 31 October 2011

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

Presented in part at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium, San Francisco, 20–22 January 2011.

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Published online: 17 December 2011

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

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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

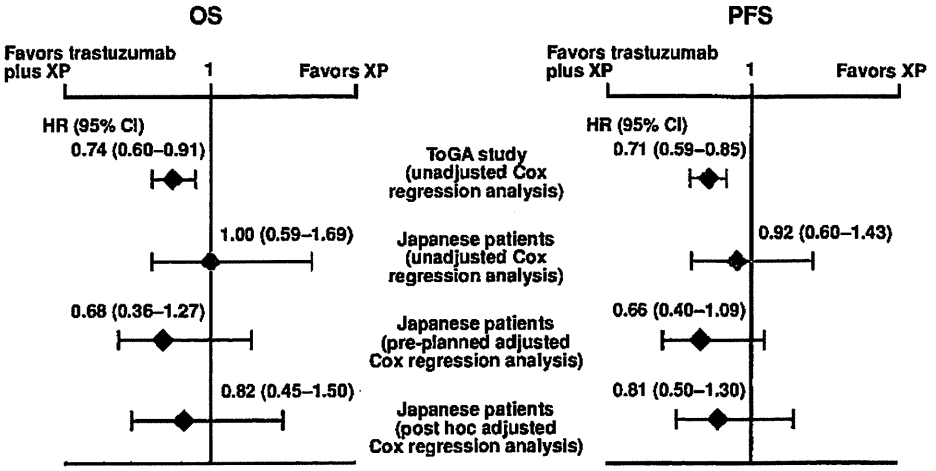

Fig. 1 Unadjusted and adjusted hazard ratios for overall and progression-free survival. *CI* confidence interval, *HR* hazard ratio, *OS* overall survival, *PFS* progression-free survival, *XP* capecitabine plus cisplatin

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

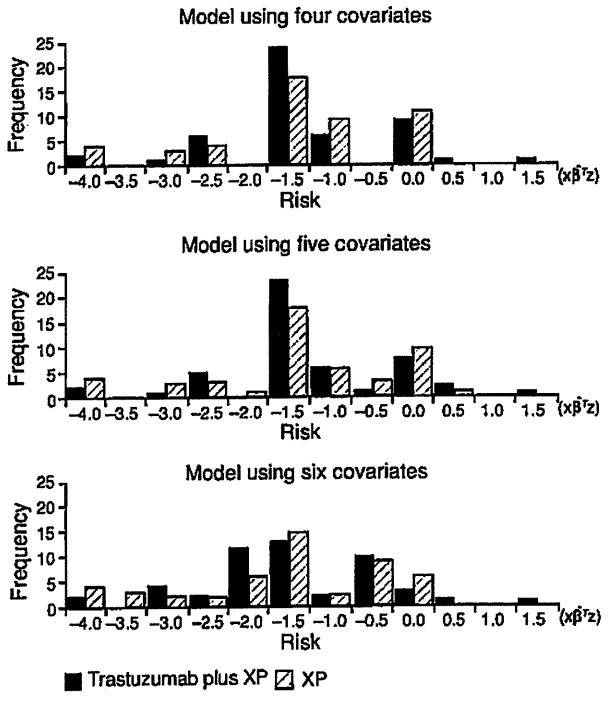

Fig. 2 Distribution of estimated values by linear predictor. *XP* capecitabine plus cisplatin. The ordinate is the number of patients and the abscissa is the risk score (estimated hazard number for each patient). The risk of mortality increases as the plot moves to the right

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.

Acknowledgments This study was sponsored by Chugai Pharmaceutical Co., Ltd. and F. Hoffmann-La Roche Ltd. We thank all of the patients and investigators who participated in the ToGA study in Japan.

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Int J Clin Oncol (2012) 17:1–29
DOI 10.1007/s10147-011-0315-2

SPECIAL ARTICLE

Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer

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Received: 18 August 2011 / Accepted: 25 August 2011 / Published online: 15 October 2011

Abstract Colorectal cancer is a major cause of death in Japan, where it accounts for the largest number of deaths from malignant neoplasms in women and the third largest number in men. Many new treatment methods have been developed over the last few decades. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer (JSCCR Guidelines 2010) have been prepared to show standard treatment strategies for colorectal cancer, to eliminate disparities among institutions in terms of treatment, to eliminate unnecessary treatment and insufficient treatment, and to deepen mutual understanding between health-care professionals and patients by making these Guidelines available to the general public. These Guidelines have been prepared by consensuses reached by the JSCCR Guideline Committee, based on a careful review of the evidence retrieved by literature searches and in view of the medical health insurance system and actual clinical practice settings in Japan. Therefore, these Guidelines can be used as a tool for treating colorectal cancer in actual clinical practice settings. More specifically, they can be used as a guide to

This article was originally appeared in Japanese as *Daicho gan chiryo gaidorain · Ishiyo 2010 nen ban* (JSCCR Guidelines 2010 for the Treatment of Colorectal Cancer), published by Kanehara, Tokyo, 2010.

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obtaining informed consent from patients and choosing the method of treatment for each patient. As a result of the discussions held by the Guideline Committee, controversial issues were selected as Clinical Questions, and recommendations were made. Each recommendation is accompanied by a classification of the evidence and a classification of recommendation categories based on the consensus reached by the Guideline Committee members. Here we present the English version of the JSCCR Guidelines 2010.

Keywords Colorectal cancer · Guideline · Treatment · Surgery · Chemotherapy · Endoscopy · Radiotherapy · Palliative care · Surveillance

Introduction

1. Guideline objectives

Mortality and morbidity from colorectal cancer have substantially increased in Japan recently. According to the vital statistics for Japan in 2008, colorectal cancer accounted for the largest number of deaths from malignant neoplasms in women and the third largest number in men, after lung cancer and gastric cancer. Nevertheless, the number of deaths from colorectal cancer per unit population has increased approximately tenfold during the past 50 years. Many new treatment methods have been developed during that time, and their use in combination with advances in diagnostic methods has led to a steady improvement in the results of treatment. However, there are differences in treatment among medical institutions in Japan that provide medical care for patients with colorectal cancer, and these differences may lead to differences in the results of treatment.

Under such circumstances, the JSCCR guidelines 2010 for the treatment of colorectal cancer (JSCCR Guidelines 2010), which are intended for doctors (general practitioners and specialists) who provide medical care for patients with colorectal cancer at various disease stages and conditions, have been prepared for the following purposes: (1) to show standard treatment strategies for colorectal cancer; (2) to eliminate disparities among institutions in terms of treatment; (3) to eliminate unnecessary treatment and insufficient treatment; and (4) to deepen mutual understanding between health-care professionals and patients by making these Guidelines available to the general public [1].

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The following are expected to be achieved with these Guidelines: (1) improved treatment of colorectal cancer in Japan; (2) improved results of such treatment; (3) reduced human and financial burdens; and (4) increased benefits for patients.

2. How to use these Guidelines

These Guidelines have been prepared by consensuses reached by the JSCCR Guideline Committee, based on a careful review of the evidence retrieved by literature searches and in view of the medical health insurance system and actual clinical practice settings in Japan, so these Guidelines can be used as a tool for treating colorectal cancer in actual clinical practice settings. More specifically, they can be used as a guide to obtaining informed consent from patients and choosing the method of treatment for each patient. However, these Guidelines provide only general recommendations for choosing treatment strategies for colorectal cancer, and they do not control or limit treatment strategies or treatment methods that are not described herein. These Guidelines can also be used as a document to explain the rationale for selecting treatment strategies and treatment methods that differ from those described in these Guidelines.

JSCCR is responsible for the statements in these Guidelines. However, the personnel directly in charge of treatment, not the JSCCR or the Guideline Committee, are responsible for the outcome of treatment.

3. Method used to prepare these Guidelines

(1) Classification of evidence

Levels of evidence were classified as "high-level evidence" or "low-level evidence" as follows:

[High-level evidence]

- Meta-analyses of systematic reviews/randomized controlled trials (RCTs),
- randomized controlled trials,
- nonrandomized controlled trials,
- cohort studies, case–control studies, and cross-sectional studies.

[Low-level evidence]

- Case series studies, case studies, expert opinions, and clinical experience.

(2) Clinical Questions and classification of recommendation categories

As a result of the discussions held by the Guideline Committee, controversial issues were selected as Clinical Questions (CQ), and recommendations were made.

Each recommendation in response to a CQ is accompanied by a classification of the evidence and a classification of recommendation categories based on the consensus reached by the Guideline Committee members. In determining the recommendation categories, in addition to an evaluation of the internal validity of the source of evidence for each recommendation, a comprehensive investigation of the internal validity, external validity, and clinical applicability of each recommendation was performed, considering the following points: (1) the treatment method has a clear scientific rationale and is the best treatment method conceivable; (2) the treatment method is as safe as possible, causes little invasion, and maintains physical function; (3) the treatment method is cost-effective and imposes the smallest financial burden on the patient; and (4) the treatment method is in line with the treatment methods used in actual clinical practice settings in Japan.

Recommendations with which all members of the Guideline Committee agreed were classified as category A or category B recommendations. Recommendations with which three or more members of the Committee disagreed were classified as category D recommendations, and all other recommendations were classified as category C recommendations. The category D recommendations are not included in these Guidelines.

Classification of recommendation categories:

- Category A: unanimous recommendations by the Guideline Committee based on high-level evidence
- Category B: unanimous recommendations by the Guideline Committee based on low-level evidence
- Category C: recommendations that were not agreed to completely by the members of the Guideline Committee, irrespective of the level of evidence
- Category D: recommendations that were not agreed to by three or more members of the Guideline Committee

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Table 1 Number of scientific articles retrieved and selected

	Number of articles retrieved		Number of articles selected		Number of articles retrieved manually
	PubMed	Ichushi	PubMed	Ichushi	
(1) Endoscopic treatment of colorectal cancer	283	214	10	8	8
(2) Treatment of stage 0 to stage III colorectal cancer	347	268	49	11	2
(3) Treatment of stage IV colorectal cancer	189	98	79	14	9
(4) Treatment of liver metastases of colorectal cancer	645	281	255	42	14
(5) Treatment of lung metastases of colorectal cancer	54	134	28	22	2
(6) Treatment of recurrent colorectal cancer	488	125	111	18	7
(7) Adjuvant chemotherapy for colorectal cancer	340	189	154	27	31
(8) Chemotherapy for unresectable colorectal cancer	472	66	234	41	121
(9) Adjuvant radiotherapy for colorectal cancer	398	61	86	6	15
(10) Palliative radiotherapy for colorectal cancer	704	31	107	6	17
(11) Palliative care for colorectal cancer	182	58	19	5	8
(12) Surveillance after surgery for colorectal cancer	1,203	1,213	249	37	13
Total	5,305	2,738	1,381	237	247

4. Literature search

Initially, the literature search was performed for the following 12 broad categories. Then, a further search was done as needed with additional search techniques.

(1) Endoscopic treatment of colorectal cancer
(2) Treatment of stage 0 to stage III colorectal cancer
(3) Treatment of stage IV colorectal cancer
(4) Treatment of liver metastases of colorectal cancer
(5) Treatment of lung metastases of colorectal cancer
(6) Treatment of recurrent colorectal cancer
(7) Adjuvant chemotherapy for colorectal cancer
(8) Chemotherapy for unresectable colorectal cancer
(9) Adjuvant radiotherapy for colorectal cancer
(10) Palliative radiotherapy for colorectal cancer
(11) Palliative care for colorectal cancer
(12) Surveillance after surgery for colorectal cancer

The PubMed and Ichushi-Web databases were selected for the search, and the English and Japanese literature was searched in both databases for the period from January 1983 to December 2007. The task of searching was shared by four members of the medical library; the four members created a search formula by discussion with the Committee members in charge of each item and collected literature during the search period (January 2008 to July 2008). For categories (7) and (8), however, April 2010 was set as the end of the search period. In addition, secondary documents such as UpToDate and literature collected by manual searching were added and critically examined as needed, and other documents such as minutes and guidelines were included as necessary. Of the 8,043 references identified as a result of the searches (5,305 in the PubMed database and 2,738 in the Ichushi-Web database), 1,618 references were retrieved and examined critically (Table 1).

5. Funding

Preparation of these Guidelines was funded by the JSCCR and the Health and Labour Sciences Research Fund (3rd Term Comprehensive 10-Year Strategy for Cancer Control Research Project).

6. Conflicts of interest

None of the members of the committee in charge of the preparation of these Guidelines has any conflict of interest with entities such as any specific profit or nonprofit organizations or any entities related to pharmaceutical or medical products, and the board of the JSCCR confirmed the self-reported absence of any conflicts of interest by the Guideline Committee members.

Treatment guidelines for colorectal cancer

Chapter 1: Treatment strategies for stage 0 to stage III colorectal cancer

1. Endoscopic treatment

General principles underlying the indications for endoscopic resection (Fig. 1)

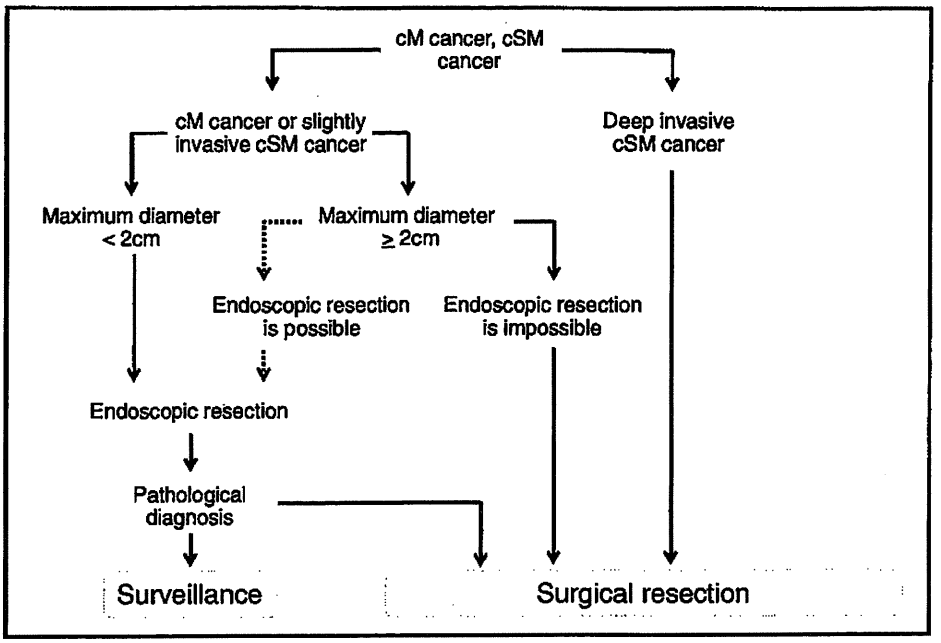

Fig. 1 Treatment strategies for cM cancer and cSM cancer

- There is little possibility of lymph node metastasis, and the size and location of the tumor make en bloc resection possible.

Indication criteria for endoscopic resection:

(1) Intramucosal carcinoma or carcinoma with slight submucosal invasion
(2) Maximum diameter <2 cm
(3) Any macroscopic type

- Endoscopic treatment is a method of endoscopically resecting lesions in the large bowel and of collecting the resected specimens.
- Endoscopic treatment methods consist of polypectomy,[1] endoscopic mucosal resection (EMR),[2] and endoscopic submucosal dissection (ESD).[3]
- In determining the indication for endoscopic treatment and the treatment method, information on the size, predicted depth of invasion, and morphology of the tumor is essential, and the histological type of the tumor should also be taken into consideration.

Comments

- Endoscopic resection is intended for both diagnosis and treatment. It consists of total excisional biopsy in which curability and the need for additional intestinal resection are assessed by histopathological examination of the resected specimens (CQ-1).
- En bloc resection is desirable for accurate diagnosis of the status of carcinoma invasion in the resection margin and the deepest area.
- 2 cm is the largest size of a tumor that can be easily resected en bloc by polypectomy or snare EMR [3] (CQ-2).
- Colorectal ESD has not become a common treatment method, because the technique is difficult and there is a high risk of complications (perforation) [3].
- EMRC (EMR using a cap) involves a high risk of perforation when used for colon lesions.
- If the preoperative diagnosis is intramucosal carcinoma, piecemeal resection can be performed. It should be noted, however, that piecemeal resection is associated with a high incomplete resection rate and a high local recurrence rate [3].

2. *Surgical treatment (Fig. 2)*

- The extent of lymph node dissection to be performed during colorectal cancer surgery is determined based on the preoperative clinical findings (c) or on the extent of

[1] In polypectomy, a snare is placed on the stalk of the lesion, and the lesion is electrocauterized using a high-frequency current. This method is mainly used for protruding lesions.

[2] In EMR, the lesion is elevated through the local injection of a liquid such as physiological saline into the submucosa, and the lesion is electrocauterized just as in polypectomy. This method comprises the snare method [2] and EMR using a cap (EMRC). It is mainly used for superficial tumors and large sessile lesions.

[3] In ESD, the lesion is elevated through the local injection of a liquid such as sodium hyaluronate solution into the submucosa of the perilesional area; then, circumferential incision of the mucosa surrounding the lesion and dissection of the submucosa are performed with a special knife [3]. ESD is mainly indicated for large tumors that cannot be resected by EMR.