Randomized clinical trial of adjuvant chemotherapy with intraperitoneal and intravenous cisplatin followed by oral fluorouracil (UFT) in serosa-positive gastric cancer versus curative resection alone: final results of the Japan Clinical Oncology Group trial JCOG9206-2

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Abstract

Purpose To evaluate the survival benefit of adjuvant chemotherapy after curative resection in serosa-positive gastric cancer, a multicenter phase III clinical trial was conducted in Japan.

Patients and methods From January 1993 to March 1998, 268 patients were randomized to adjuvant chemotherapy (135 patients) or surgery alone (133 patients). All patients underwent gastrectomy with D2 or greater lymph node dissection. The chemotherapy regimen consisted of intraperitoneal cisplatin soon after abdominal closure, postoperative intravenous cisplatin (day 14) and 5-fluorouracil (day 14–16), and daily oral FU (UFT) starting 4 weeks

after surgery for 12 months. The primary endpoint was overall survival. Relapse-free survival and site of recurrence were secondary endpoints.

Results Fifty-two patients (38.5%) in the adjuvant chemotherapy arm completed the chemotherapy regimen. There were 4 (1.49%) treatment-related deaths, 1 in the surgery-alone and 3 in the adjuvant chemotherapy arm (2 did not receive chemotherapy). Grade 4 toxicity was observed in 3 patients in the surgery-alone and 2 patients in the adjuvant chemotherapy arm. There was no significant difference in 5-year overall survival (62.0% adjuvant chemotherapy vs. 60.9% surgery-alone, $P = 0.482$) and 5-year relapse-free survival rates (57.5% adjuvant chemotherapy vs. 55.6% surgery-alone; $P = 0.512$).

Conclusion There was no benefit in overall and relapse-free survival with this adjuvant chemotherapy regimen for

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patients with macroscopically serosa-positive gastric cancer after curative resection.

Keywords Randomized clinical trial · Adjuvant chemotherapy · Serosa-positive gastric cancer · Intraperitoneal chemotherapy

Introduction

A large number of gastric cancers are still diagnosed in advanced stages worldwide [1, 2]. Once the primary tumor invades the subserosal or serosal layers of the gastric wall, cancer cells are more likely to spread into the abdominal cavity and implant on peritoneal surfaces, resulting in peritoneal dissemination [3, 4]. The most frequent cause of recurrence and subsequent cancer death in serosa-positive gastric cancer is peritoneal metastasis even after curative resection [5–7]. The main goal of adjuvant chemotherapy for resected gastric cancer is to prevent such a distant recurrence and increase the potential of cure.

In Japan today, adjuvant chemotherapy with single agent S-1 is considered the standard of care for patients with pathological stage II/III (Japanese Classification of Gastric Carcinoma 2nd English Edition [8, 9]) gastric cancer after potentially curative D2 dissection, based on the results of the ACTS-GC clinical trial [10–13]. However, subgroup analysis of the ACTS-GC data suggest that S-1 may be less effective for patients with more advanced gastric cancer such as serosa-positive cancer.

The present Japan Clinical Oncology Group (JCOG) trial, JCOG9206-2, is a randomized controlled phase III clinical trial of adjuvant chemotherapy with intraperitoneal and intravenous cisplatin followed by oral fluorouracil (FU). Thirteen institutions in Japan participated in this trial as members of the Gastric Cancer Surgical Study Group (GCSSG), a subgroup of JCOG [14]. We report here the final results with 6 years of follow-up.

Patients and methods

Patients

Patients had to fulfill the following eligibility criteria: macroscopically complete operation; histologically proven gastric adenocarcinoma, macroscopically serosa-positive (T3–4), with no metastases to level 3–4 lymph node stations (N0–2) [8, 9]; age 75 years or younger; no previous treatment for gastric cancer; negative peritoneal lavage cytology; adequate organ function as assessed by laboratory studies: leukocyte count of at least 4000/mm³; hemoglobin of at least 11.0 g/dl; platelet count of at least

100000/mm³; AST, ALT, total bilirubin, blood urea nitrogen and creatinine no higher than 1.25 times the upper limit of normal; creatinine clearance no lower than 70 ml/min. All patients provided written informed consent. Patients who had undergone any chemotherapy or radiotherapy, or those with synchronous or metachronous cancer of other organs were excluded.

Treatment assignment and evaluation

The patients were randomized using the minimization method to balance the adjuvant chemotherapy and surgery-alone arms according to institution and the combination of the macroscopic depth of tumor invasion (T-category) and lymph node metastasis (N-category) according to the Japanese Classification of Gastric Carcinoma 2nd English Edition [9]. After the surgeon confirmed the above eligibility criteria, patients were randomly assigned to either arm by means of an intraoperative telephone call to the JCOG Data Center (Fig. 1).

The chemotherapy comprised intraperitoneal cisplatin (70 mg/m²) soon after abdominal closure; intravenous cisplatin (70 mg/m²) on postoperative day 14; intravenous 5-fluorouracil (5-FU) (700 mg/m²) daily on postoperative days 14–16; and UFT (267 mg/m²) daily, starting 4 weeks after surgery for 12 months. Intraperitoneal cisplatin (70 mg/m² with saline in total volume 1000 ml) was administered via drainage tubes that were clamped for following 2 h. Creatinine clearance was evaluated twice weekly before and after the administration of cisplatin. A full blood count was performed every week to assess for hematological toxicity during hospital stay. During UFT treatment, each patient was asked to visit the hospital every month for physical examinations and laboratory testing in both arms. Patients underwent upper gastrointestinal series, gastric endoscopy, ultrasonography, computed tomography or other investigations either as required or every 6 months

Fig. 1 Study scheme. All patients underwent gastrectomy with D2 or greater lymph node dissection. CDDP, *cis*-diamminedichloro-platinum (cisplatin)

to evaluate for recurrence. Adverse events were recorded according to the JCOG toxicity criteria [15]. Since some adverse events may occur after surgery even without chemotherapy, all potential adverse drug effects were compared with the adverse effects experienced by patients in the surgery-alone arm. Data on adverse events in the surgery-alone patients, except for postoperative morbidity and mortality, were collected retrospectively. Original case report forms were designed to collect adverse events during chemotherapy (only in the adjuvant chemotherapy arm). However, some adverse events happened even in the surgery-alone group. To keep the comparability between arms, we re-collected the data of adverse events from both arms at the final analysis. The surgery-alone arm received no additional treatment after surgery unless there was recurrence. The main prognostic factors, including age, gender, the depth of tumor invasion and nodal spread, operative procedures, and pathological findings, were described according to the general guidelines issued by the Japanese Research Society for Gastric Cancer Study [8, 9].

Study design and statistical analyses

This study was designed as a multicenter prospective randomized controlled phase III clinical trial. The study protocol was approved by the JCOG Clinical Trial Review

Committee and the institutional review boards of all participating institutions. The primary endpoint was OS. Relapse-free survival and the site of recurrence were secondary endpoints. The original planned duration of accrual was 4 years with 5 years of follow-up. The planned sample size was 280 patients, with 140 patients in each arm to power the study at 80% to detect a 15% difference in 5-year OS rates between the surgery-alone arm (40%) and the chemotherapy arm (55%) with a two-sided significance level of 5%. The study design was amended to one projecting 5-year OS rates of 55% in the surgery-alone arm and 67% in the chemotherapy arm, with a 5-year accrual period and 6 years follow-up, because combined survival was better, and accrual poorer, than expected.

OS was measured from the date of random treatment assignment to the date of death or censored at the date of the last follow-up. Relapse-free survival was measured from the date of random treatment assignment to the date of the first observation of relapse or the date of death from any cause. If no progression was reported and if the patient remained alive, data on relapse-free survival were censored as of the date on which the absence of relapse was confirmed. OS and relapse-free survival were estimated by the Kaplan–Meier method and compared by the stratified log-rank test with the combination of the depth of the tumor invasion and lymph node metastasis as strata on the

Fig. 2 CONSORT diagram

Table 1 Distribution of the main prognostic factors in the two treatment arms

No. of patients	Surgery (<i>n</i> = 133)	Surg + Cx (<i>n</i> = 135)	<i>P</i> *
Gender			0.601
Male	88	94	
Female	45	41	
Age (years)			0.043
Median	57	59	
Range	23–73	33–75	
Tumor diameter (cm)			0.324
Median	5.5	6.0	
Range	2.4–19.0	1.5–18.0	
Macroscopic type			0.603
0	0	0	
1	5	1	
2	31	32	
3	76	78	
4	14	15	
5	7	9	
Liver metastasis			–
Absent (H0)	133	135	
Present (H1)	0	0	
Peritoneal metastasis (macroscopic)			0.245
Absent (P0)	131	135	
Present (P1)	2	0	
Type of gastrectomy			1.000
Total	76	76	
Proximal	0	1	
Distal	57	58	
Combined resection			0.787
No	39	37	
Yes	94	98	
Spleen	73	74	
Pancreas	26	26	
Adrenal gland	7	5	
Colon	6	6	
Other	50	50	
Pathological depth of tumor invasion (T)			0.613
T1			
m, sm	2	3	
T2			
mp	5	7	
T2			
ss	34	41	
T3			
se	88	77	
T4			
si	4	7	

Table 1 continued

No. of patients	Surgery (<i>n</i> = 133)	Surg + Cx (<i>n</i> = 135)	<i>P</i> *
Pathological extent of lymph node metastasis (N) ^a			0.794
N0	32	41	
N1	51	49	
N2	38	35	
N3	5	4	
N4	7	5	
Involvement of the resection margin			1.000
Proximal			
Negative	133	134	
Positive	0	1	
Distal			0.498
Negative	133	133	
Positive	0	2	
Tumor histology			0.991
Common types			
Papillary	1	2	
Well differentiated	10	12	
Moderately differentiated	33	35	
Poorly differentiated	69	67	
Mucinous	6	5	
Signet ring cell	13	13	
Other types			
Carcinoid	1	0	
Unknown	0	1	

Surg + Cx Surgery plus adjuvant chemotherapy, *m* mucosa including muscularis mucosae, *sm* submucosa, *mp* muscularis propria, *ss* subserosal, *s* serosa, *si* serosa-infiltrating

* A *t*-test was used for continuous variables. Fisher's exact test was used for discrete variables

^a Pathological extent of lymph node metastasis was classified based on the Japanese Classification of Gastric Carcinoma 1st English edition. Data are missing for one patient in the Surg + Cx arm

intention-to-treat basis. Analyses for toxicity were conducted for all of the randomly assigned patients. All statistical analyses were conducted with SAS software (version 8.1, SAS Institute, Cary, NC).

Results

From January 1993 to March 1998, 268 patients were enrolled in this phase III study. Of the 268 eligible patients enrolled, 133 patients were assigned to the surgery-alone arm and 135 patients to the adjuvant chemotherapy arm (Fig. 2). Distribution of the main prognostic factors across the two arms was well balanced (Table 1). There were no significant differences between the two groups in the

Table 2 Frequency of postoperative morbidity and mortality

	Surgery (<i>n</i> = 133)	Surg + Cx (<i>n</i> = 135)	<i>P</i>
Surgical morbidity			
Leakage	3	9	0.137
Pancreatic fistula	20	14	0.275
Peritoneal abscess	8	13	0.364
Pneumonia	3	1	0.369
Other infections	9	6	0.439
Stomal stenosis	2	1	0.621
Ileus	0	4	0.122
Miscellaneous	4	16	0.009
Non-surgical morbidity			
Creatinine ≥ 2.0	3	21	<0.001
AST, ALT ≥ 100	44	43	0.896
Hospital death	1	4	0.370

Surg + Cx Surgery plus adjuvant chemotherapy

institution and the combination of macroscopic T-category and N-category as stratification factors. There were also no significant differences in gender, but the surgery-alone group was younger than the adjuvant chemotherapy group ($P = 0.0426$). All patients underwent gastrectomy with D2 or greater lymph node dissection. The operative procedures were similar in the two groups. Seventy-six of 133 patients (57.1%) in the surgery-alone arm and 76 of 135 (56.3%) in the adjuvant chemotherapy arm underwent total gastrectomy, and all the other patients except one underwent distal gastrectomy. Similar numbers of patients in each group underwent combined resections involving the spleen, pancreas, adrenal gland, colon or other organs. There were no significant differences between the two groups in tumor diameter, macroscopic type, presence of liver or macroscopic peritoneal metastasis, depth of tumor invasion, extent of lymph node metastasis, involvement of the resection margins and histological type.

Of the 135 patients of the adjuvant chemotherapy arm, 82 patients discontinued chemotherapy as is shown in Fig. 2. Thirty-two patients discontinued chemotherapy because of toxicity, among whom 19 patients could not start intravenous chemotherapy. Therefore, only the remaining 13 patients terminated chemotherapy during intravenous CDDP/5-FU or oral UFT.

The perioperative mortality was low. There were 4 treatment-related deaths. One of 133 patients in the surgery-alone arm died because of postoperative complications, and 3 of 135 in the adjuvant chemotherapy arm died because of postoperative complications or chemotherapy toxicity (2 of 3 did not receive chemotherapy). There were no significant differences in the frequency of surgical morbidity except for miscellaneous events such as wound

Table 3 Adverse events

Arm	Grade ^a					% Grade 4	Total
	0	1	2	3	4		
Surgery							
Leukopenia	90	28	9	0	0	0	127
Anemia	58	31	34	4	–	–	127
Thrombocytopenia	125	1	1	0	0	0	127
Increase in bilirubin	83	–	32	11	1	0.8	127
Increase in AST	22	62	27	14	2	1.6	127
Increase in ALT	26	55	29	16	1	0.8	127
Increase in creatinine	109	13	4	1	0	0	127
Nausea or vomiting	110	16	4	0	0	0	130
Diarrhea	122	6	2	0	0	0	130
Stomatitis	129	1	0	0	0	0	130
Neuropathy (sensory)	130	0	0	0	0	0	130
Skin-other (pigmentation)	130	0	0	0	0	0	130
Surg + Cx							
Leukopenia	76	30	19	3	1	0.8	129
Anemia	31	24	56	18	–	–	129
Thrombocytopenia	123	4	1	0	1	0.8	129
Increase in bilirubin	67	–	43	15	1	0.8	126
Increase in AST	25	61	27	16	0	0	129
Increase in ALT	29	70	21	9	0	0	129
Increase in creatinine	70	38	16	5	0	0	129
Nausea or vomiting	80	31	19	1	0	0	131
Diarrhea	113	17	1	0	0	0	131
Stomatitis	126	4	1	0	0	0	131
Neuropathy (sensory)	128	3	0	0	0	0	131
Skin-other (pigmentation)	130	1	0	0	0	0	131

Surg + Cx Surgery plus adjuvant chemotherapy

^a Toxicity graded according to JCOG criteria [13]

infection (Table 2). As for postoperative non-surgical morbidity, renal dysfunction (JCOG grade 3–4) within 3 months after surgery was observed only in 5 patients in the adjuvant chemotherapy group. Adverse events were generally mild. The frequencies of adverse events according to JCOG criteria are listed in Table 3. Grade 4 toxicity was observed in 3 patients in the surgery-alone and 2 patients in adjuvant chemotherapy arm.

In 6 years of planned follow-up, there was no significant differences in OS (Fig. 3) and relapse-free survival (Fig. 4). The 5-year overall survival rate in the adjuvant chemotherapy arm was 62.0% (95% confidence interval 53.7–70.2) versus 60.9% (52.6–69.2) in the surgery-alone arm ($P = 0.482$, one-sided stratified log-rank test). The 5-year relapse-free survival rate was 57.5% (49.1–65.9) in the adjuvant chemotherapy group versus 55.6% (47.2–64.1) in the surgery-alone group ($P = 0.512$ one-sided stratified log-rank test). Sixty-six of 135 patients (48.9%) in the adjuvant chemotherapy arm and 64 of 133 patients

Fig. 3 Overall survival. There was no significant difference in overall survival: 5-year survival rate 62.0% (95% confidence interval 53.7–70.2) in the adjuvant chemotherapy group versus 60.9% (52.6–69.2) in the surgery-alone group, $P = 0.482$

Fig. 4 Relapse-free survival. There was no significant difference in relapse-free survival: 5-year relapse-free survival rate 57.5% (95% confidence interval 49.1–65.9) in the adjuvant chemotherapy group versus 55.6% (47.2–64.1) in the surgery-alone group, $P = 0.512$

(48.1%) in the surgery-alone arm experienced cancer recurrence or death. The results for survival were not substantially changed after adjustment for age by Cox proportional hazards regression. Sites of recurrence, including peritoneal dissemination as the most common site, did not differ significantly between the two arms (Table 4).

Discussion

The present study is a prospective randomized controlled phase III clinical trial of adjuvant chemotherapy with cisplatin followed by UFT conducted by the GCSSG subgroup of JCOG to clarify the efficacy of adjuvant

Table 4 Site of cancer recurrence

Site of recurrence	Surgery (<i>n</i> = 133)	Surg + Cx (<i>n</i> = 135)	Total
Peritoneal dissemination	23	19	42
Liver metastases	9	16	25
Metastases to other organs	5	7	12
Local (remnant stomach)	0	2	2
Local (other sites)	4	2	6
Distant lymph nodes	10	6	16
Other	5	0	5
Death before recurrence	8	14	22
Total	64	66	130

Surg + Cx Surgery plus adjuvant chemotherapy

chemotherapy after curative resection with extended (D2 or greater) lymphadenectomy for macroscopically serosa-positive gastric cancer. There was no benefit in overall and relapse-free survival with this regimen, and there was no difference between the arms in the site of recurrence. The frequency of postoperative morbidity was similar in the two groups, suggesting that administration of intraperitoneal cisplatin does not affect postoperative morbidity [16].

The recent AMC 0101 trial demonstrated that adjuvant chemotherapy with intraperitoneal cisplatin and early mitomycin-C plus long-term doxifluridine plus cisplatin (iceMFP) improved survival of patients with grossly serosa-positive advanced gastric cancer when compared with mitomycin-C plus short-term doxifluridine (Mf) [17]. Another Korean randomized trial, AMC 0201, showed there was no benefit in survival with adjuvant mitomycin-C plus long-term doxifluridine plus cisplatin when compared with Mf [18]. Taken together, these two studies suggest that improved OS might have been due to intraperitoneal cisplatin and/or mitomycin-C when given early. However, the AMC 0101 trial could not definitively demonstrate whether intraperitoneal chemotherapy itself contributed to improved survival. The adjuvant chemotherapy in the present study might be insufficient because it consisted of just one single course of intravenous cisplatin/5-FU. However, in the AMC 0201 trial, repeated administration of doxifluridine plus cisplatin did not show any benefit over short-term mitomycin-C plus doxifluridine.

Only 39% in the adjuvant chemotherapy arm actually completed the chemotherapy regimen in the present study, although UFT toxicity was generally mild. Patients tend to suffer from gastrointestinal disturbances after gastrectomy even without postoperative chemotherapy. Compliance of highly toxic regimens significantly decreases if given in early postoperative period, as observed in the MAGIC trial, which demonstrated the superiority in overall survival of pre- and postoperative chemotherapy compared with

surgery-alone [19]. The MAGIC trial reported that 57% of patients in the chemotherapy group were able to receive postoperative chemotherapy and that only 43% of patients in the chemotherapy group actually completed the full 6 cycles, although 88% of patients completed the 3 cycles of neoadjuvant chemotherapy. Thus, special consideration should be given to compliance when choosing a regimen for postoperative adjuvant chemotherapy. Powerful regimens should be planned for neoadjuvant settings in more advanced disease and less toxic drugs for postoperative use for earlier stage disease, such as stage II [12, 20, 21].

In conclusion, there was no benefit in overall and relapse-free survival with adjuvant cisplatin followed by UFT for patients with macroscopically serosa-positive gastric cancer after curative resection. When recurrence occurs, there was no difference in the site between the two treatment groups. Therefore, we do not recommend adjuvant chemotherapy with this regimen for this patient population in clinical practice.

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