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Phase III trial of adjuvant 5-fluorouracil and adriamycin versus 5-fluorouracil, adriamycin, and polyadenylic–polyuridylic acid (poly A:U) for locally advanced gastric cancer after curative surgery: final results of 15-year follow-up

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Background: This phase III trial was to compare 5-fluorouracil (5-FU), adriamycin, and polyadenylic–polyuridylic acid (poly A:U) against 5-fluorouracil plus adriamycin (FA) for operable gastric cancer.

Patients and methods: From 1984 to 1989, patients who had $D_{2–3}$ curative resection were randomly assigned to receive chemotherapy or chemoimmunotherapy. Chemotherapy consisted of 12 mg/kg 5-FU every week for 18 months and 40 mg/m^2 adriamycin every 3 weeks for 12 cycles. Chemoimmunotherapy consisted of FA plus 100 mg of poly A:U weekly for six cycles and was followed 6 months later by six weekly 50-mg booster injections.

Results: A total of 292 patients were enrolled. After excluding 12 ineligible patients, 142 and 138 patients were allocated to each treatment. Patients were balanced with prognostic variables: age, sex, tumor location, differentiation, degree of tumor invasion (T_2–T_{4a}), and lymph node status (N_0–N_2). During the 15-year follow-up, chemoimmunotherapy significantly prolonged overall ($P = 0.013$) and recurrence-free ($P = 0.005$) survivals compared with chemotherapy alone. The survival benefits were prominent in the subset of patients with T_3/T_{4a}, N_2, or stage III. Treatments were generally well tolerated in both arms.

Conclusions: These results indicate a survival advantage of chemoimmunotherapy with a regimen of FA and poly A:U in curatively resected gastric adenocarcinoma.

Key words: adjuvant chemotherapy, chemoimmunotherapy, gastric cancer, poly A:U

introduction

Gastric cancer remains a worldwide health problem [1]. In Korea, gastric cancer is the leading cause of cancer-related deaths [2]. The most effective treatment for gastric cancer is radical gastrectomy. A substantial number of patients, however, eventually die of recurrence after curative resection. In an attempt to improve the survival of gastric cancer patients who have undergone curative resection, a number of randomized trials have investigated the role of adjuvant chemotherapy or immunotherapy. Meta-analyses on adjuvant chemotherapy for gastric cancer have indicated that adjuvant chemotherapy does not significantly increase survival in Western populations, but it does have an effect on Asian populations [3, 4]. At the initiation of the present trial, Moertel et al. [5] indicated that the combination of 5-fluorouracil (5-FU) and adriamycin would result in the most favorable survival rate for patients with advanced gastric cancer. Thus, beginning in the early 1980s, our institution treated patients who had locally advanced gastric cancer with 5-fluorouracil plus adriamycin (FA) as the adjuvant chemotherapy.

Polyadenylic–polyuridylic acid (poly A:U), a nontoxic, synthetic double-stranded complex of polyribonucleotides, has proved to be a potent immunomodulator for both humoral and cell-mediated immune responses [6–8]. The first adjuvant trial of poly A:U in human cancer was conducted on patients with operable breast cancer and demonstrated a significant survival benefit over surgery alone [9]. Moreover, poly A:U, in addition to chemotherapy, has been shown to exert a synergistic antitumor effect in experimental tumor models [10]. For gastric cancer, no immunomodulatory role of poly A:U has yet been identified. To examine the effect of poly A:U

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on gastric cancer, we conducted a prospective phase III trial of FA plus poly A:U chemoimmunotherapy versus FA chemotherapy alone after curative resection of gastric cancer.

patients and methods

eligibility criteria

Eligibility criteria included (i) pathologically proven gastric adenocarcinoma treated by curative surgery; (ii) no history of previous chemotherapy or radiotherapy; (iii) no previous immunosuppressive treatment within 3 months of surgery; (iv) Eastern Cooperative Oncology Group performance status of less than or equal to one; (v) adequate function of bone marrow (white blood cell $\geq 4 \times 10^3/\mu l$, platelets $\geq 100 \times 10^3/\mu l$, and hemoglobin ≥ 9.0 g/dl), kidney (serum creatinine level ≤ 1.5 mg/dl), and liver (increase in serum bilirubin ≤ 2.0 mg/dl and transaminase $\leq 2 \times$ upper normal limit); (vi) no history of congestive cardiac failure (CHF); and (vii) no history of other active malignancies. Patients who had early (T_1N_{0-2}) or advanced tumors ($T_{4b}N_{0-2}$ or $T_{2-4a}N_3$) were ineligible even if these were resected *en bloc* with the primary tumor (Figure 1). Other exclusion criteria included (i) age >70 years, (ii) tumor excised from discontinuous sites, or (iii) presence of ascites. Patients were enrolled after pathologic staging was completed and the patient's postoperative condition improved to a point that would permit chemotherapy (usually 2–4 weeks of postoperation). Patients who had not sufficiently recovered by the 45th postoperative day were ineligible. All patients provided written informed consent.

curative surgery

Curative resection (D_2/D_3) was defined as stipulated by the Japanese Research Society for Gastric Cancer and includes (i) total or subtotal gastrectomy with systemic lymphadenectomy and omentectomy, (ii) no involvement of surgical stumps, (iii) sufficient lymphatic dissection (R number ≥ N number), (iv) no distant metastasis, (v) removal of involved adjacent organs and structures by combined *en bloc* resection, and (vi) no gross residual disease [11]. All surgeries were carried out by five surgeons according to the standardized resection technique in two affiliated hospitals.

pathology

Pathologic reviews were done to establish the histological subtypes, tumor differentiation, tumor depth (T), and number of total resected and metastatic lymph nodes with systemic grouping (N_0–N_2). Tumor subtypes and differentiation were evaluated according to the World Health Organization (WHO) criteria and tumor staging was made according to the tumor–node–metastasis staging system of the American Joint Cancer Committee (AJCC, 1984) [12, 13].

study design

Patients were randomly assigned to receive either chemotherapy alone or chemoimmunotherapy using random tables. Chemotherapy began within 6 weeks of surgery (Figure 2). Chemotherapy consisted of 12 mg/kg 5-FU weekly for 18 months and 40 mg/m^2 adriamycin every 3 weeks for a total of 12 cycles. In patients receiving combined chemoimmunotherapy, patients followed the FA regimen above, and poly A:U (100 mg weekly for six cycles) treatments were administered beginning 4 days after the initiation of chemotherapy. Six months later, weekly 50-mg poly A:U booster injections were administered for six cycles (Figure 2). If a patient's leukocyte count fell below $3 \times 10^3/\mu l$ or the platelet count fell below $100 \times 10^3/\mu l$, treatment was delayed until recovery.

The primary end point was overall survival (OS), and the secondary end points were recurrence-free survival (RFS), gastric cancer-specific survival, and toxicity. OS was defined as the time from randomization to death by any cause or the date at which the patient was last confirmed. RFS was defined as the time from randomization to gastric cancer recurrence or the last date at which the patient was followed up. Causes of death other than gastric cancer recurrence were considered as censoring for recurrence. Gastric cancer-specific survival duration was defined from randomization to death from gastric cancer recurrence or from toxicity of treatment.

toxicity and follow-up evaluation

Adverse effects were graded by WHO criteria [14]. At the end of the planned adjuvant therapy, a follow-up study was carried out with chest radiography, computed tomography (CT) of abdomen–pelvis, radionuclide bone scan, and esophagogastroduodenoscopy. Patients were followed up monthly for the first 3 months, every 3 months for the next 2 years, every 6 months until the 10th year after surgery, and then every year thereafter.

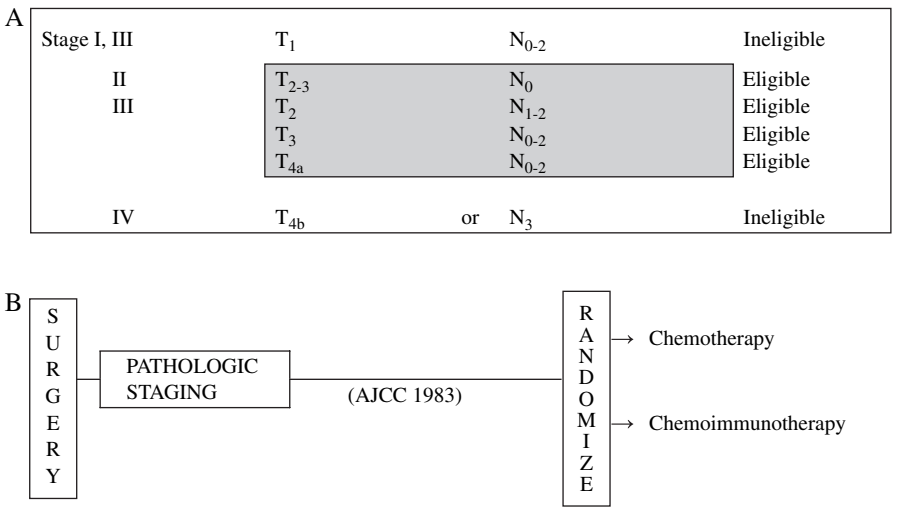

Figure 1. Eligible stages (gray area) for (A) gastric cancer [tumor–node–metastasis staging: American Joint Cancer Committee (AJCC), 1983] and (B) study design.

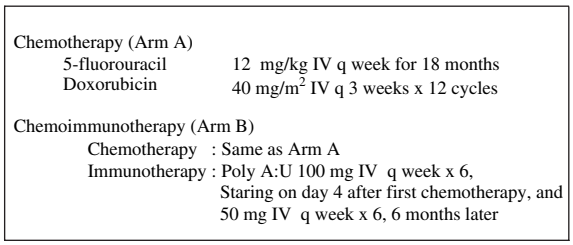

Figure 2. Treatment regimen of chemotherapy and chemoimmunotherapy.

Recurrence pattern was categorized as locoregional recurrence, peritoneal carcinomatosis, or distant metastasis. Locoregional recurrence was defined as recurrence in the gastric bed, anastomotic site, regional lymph nodes (including the paraaortic lymph nodes), or an adjacent structure by direct extension. Peritoneal carcinomatosis was based on positive cytology in ascites or visualization of peritoneal nodules by CT scan. Tumors involving ovaries (Krukenberg's tumor) were considered to be peritoneal carcinomatosis. Distant metastasis was defined as specific organ involvement via systemic metastasis. Periumbilical nodules and extra-abdominal lymph nodes were considered to be distant metastases. Newly developed tumors in the stomach remnant, except for the anastomosis site, were defined as second primary gastric cancers, which were not included in the definition of recurrence.

statistical methods

The sample size was calculated to provide the study with 80% power to detect a difference of 18% between 5-year OS rates of chemotherapy alone and chemoimmunotherapy with a two-sided α value of 0.05. It was assumed that the expected 5-year OS rate for the control group was 45%. The minimum sample size for each arm was 131, and assuming a 10% drop out rate, a final sample size for each arm was calculated to be 145 patients. All *P* values were two-sided, and the α value was set at 0.05. Survival was calculated using the Kaplan–Meier method. A log-rank test was used for multivariate analysis. The chi-square test was used to check the comparability of patient's characteristics.

results

patient characteristics

From January 1984 to December 1989, 292 patients were enrolled. Twelve patients (4.1%) were excluded due to inadequate staging; five had early gastric cancer (T_1N_{0-2}), four adjacent organ invasion (T_{4b}), and three far advanced lymph node involvement (N_3). For the adjuvant treatment, 142 and 138 patients were randomly assigned to receive chemotherapy or chemoimmunotherapy, respectively. There were no differences in age, sex ratio, tumor location, or tumor differentiation between the two treatment arms. More patients receiving chemotherapy alone, however, underwent subtotal gastrectomy ($P = 0.019$). In all, 26.8% of the chemotherapy arm were diagnosed as having T_2 cancer, as were 29.0% of the chemoimmunotherapy arm ($P = 0.278$). In all, 20.4% and 22.5% of those treated by chemotherapy and chemoimmunotherapy, respectively, were node positive ($P = 0.772$; Table 1).

treatment compliance

A complete chemotherapy regimen was administered in 95 patients (66.9%) from arm A and in 95 patients (68.8%) from arm B ($P = 0.561$). Chemotherapy was interrupted in 12 patients (8.5%) from arm A and two (1.4%) from arm B due to recurrence during treatment. In those treated by chemoimmunotherapy, 87 patients (63.0%) completed immunotherapy, while 51 patients (37.0%) did not receive the booster poly A:U.

A median of 12 cycles of adriamycin was delivered to each arm (chemotherapy: range, 2–12; chemoimmunotherapy: range, 1–12) ($P = 0.317$). The planned dose intensities for 5-FU and adriamycin were 12 mg/kg/week and 13.3 mg/m^2/week, respectively. The median relative dose intensity (RDI) for 5-FU was 0.94 (range, 0.08–1.00) and 0.97 (range, 0.12–1.00) for arms A and B, respectively ($P = 0.055$). The RDI for adriamycin was 0.87 (range, 0.36–1.00) and 0.91 (range, 0.44–1.00), respectively, for arms A and B ($P = 0.003$).

Table 1. Patient characteristics

	Chemotherapy	Chemoimmunotherapy
No. of assessable patients	142	138
Age (median)	54 (28–70)	53 (24–70)
Sex (M : F)	1.9 : 1	1.5 : 1
Tumor location, *n* (%)		
Antrum, pylorus	76 (53.5)	86 (62.3)
Body	53 (37.4)	34 (24.6)
Fundus, cardia	9 (6.3)	16 (11.6)
Diffuse	4 (2.8)	2 (1.4)
Tumor differentiation, *n* (%)		
Well differentiated	16 (11.3)	18 (13.0)
Moderately differentiated	26 (18.3)	27 (19.6)
Poorly differentiated	63 (44.4)	56 (40.6)
Signet ring cell	19 (13.4)	21 (15.2)
Undifferentiated	18 (12.6)	16 (11.6)
Type of surgery, *n* (%)		
Subtotal	115 (81.0)	95 (68.8)
Total	27 (19.0)	43 (31.2)
T stage (AJCC, 1983), *n* (%)		
T_2	38 (26.8	40 (29.0
T_3	12 (8.5)	19 (13.8)
T_{4a}	92 (64.8)	79 (57.2)
N stage (AJCC, 1983), *n* (%)		
N_0	29 (20.4)	31 (22.5)
N_1	74 (52.1	66 (47.8)
N_2	39 (27.5)	41 (29.7)
Tumor stage (AJCC, 1983), *n* (%)		
II	8 (5.6)	7 (5.1)
III	134 (94.4)	131 (94.9)

AJCC, American Joint Cancer Committee.

comparison of RFS and OS

With the median follow-up duration of 92 months (range, 7–260 months), 154 patients died: 87 (61.3%) patients of chemotherapy arm and 67 (48.6%) of chemoimmunotherapy arm. One hundred and twenty-eight patients (83.1%) died from cancer recurrence, six (3.9%) from cerebrovascular accidents, five (3.3%) from traffic accidents, four (2.6%) from heart diseases, three (1.9%) from a second primary cancer, and

eight (5.2%) from other causes. Chemoimmunotherapy arm had a longer OS compared with chemotherapy arm (68.4% at 5 years, 55.6% at 10 years, and 50.1% at 15 years versus 52.4% at 5 years, 43.8% at 10 years, and 38.1% at 15 years, respectively; $P = 0.013$; Figure 3A).

Tumor recurrence was documented in 131 patients: 77 patients (54.2%) of chemotherapy arm and 54 patients (39.1%) of chemoimmunotherapy arm. Chemoimmunotherapy arm had a longer RFS (68.3% at 5 years, 60.3% at 10 years, and 59.4% at 15 years versus 52.1% at 5 years, 46.6% at 10 years, and 44.1% at 15 years in the chemotherapy arm, respectively; $P = 0.005$; Figure 3B). Gastric cancer-specific survival rates were also higher in chemoimmunotherapy arm (70.3% at 5 years, 61.5% at 10 years, and 61.5% at 15 years versus 55.2% at 5 years, 49.0% at 10 years, and 45.6% at 15 years, respectively, in chemotherapy arm; $P = 0.005$).

Subset analyses according to tumor depth (T), lymph node involvement (N), and stage were carried out retrospectively for both RFS and OS. Subset analysis was also carried out according to 2002 AJCC staging [15] to compare these results with those of recent studies. In the T_3, T_{4a}, and N_2 subgroups, definite survival benefits ($P < 0.05$) were observed with chemoimmunotherapy when using 1983 or 2002 AJCC staging criteria. There was a marginal survival benefit in N_1 patients of chemoimmunotherapy (Table 2). Survival benefit was observed primarily for stage III disease (Figure 3; Table 2).

recurrence pattern and second primary cancer

Of the 77 recurrences in the chemotherapy arm, 53.2% were peritoneal carcinomatosis and 35.1% recurred in distant organs. Of the 54 recurrences in the chemoimmunotherapy arm, 50.0% were peritoneal carcinomatosis and 29.6% recurred in distant organs.

During the 15-year follow-up, seven and three second primary cancers arose in the chemotherapy and chemoimmunotherapy arms, respectively. Colorectal carcinoma (two patients) and a second primary gastric carcinoma (two patients) were detected most frequently in arm A and arm B, respectively.

toxicity profiles

In both arms, the most common non-hematological toxic effects of the treatments were alopecia, nausea, and vomiting. Fever was more common in the chemoimmunotherapy arm (18 versus 3). Grade 3/4 leucopenia was observed in three and

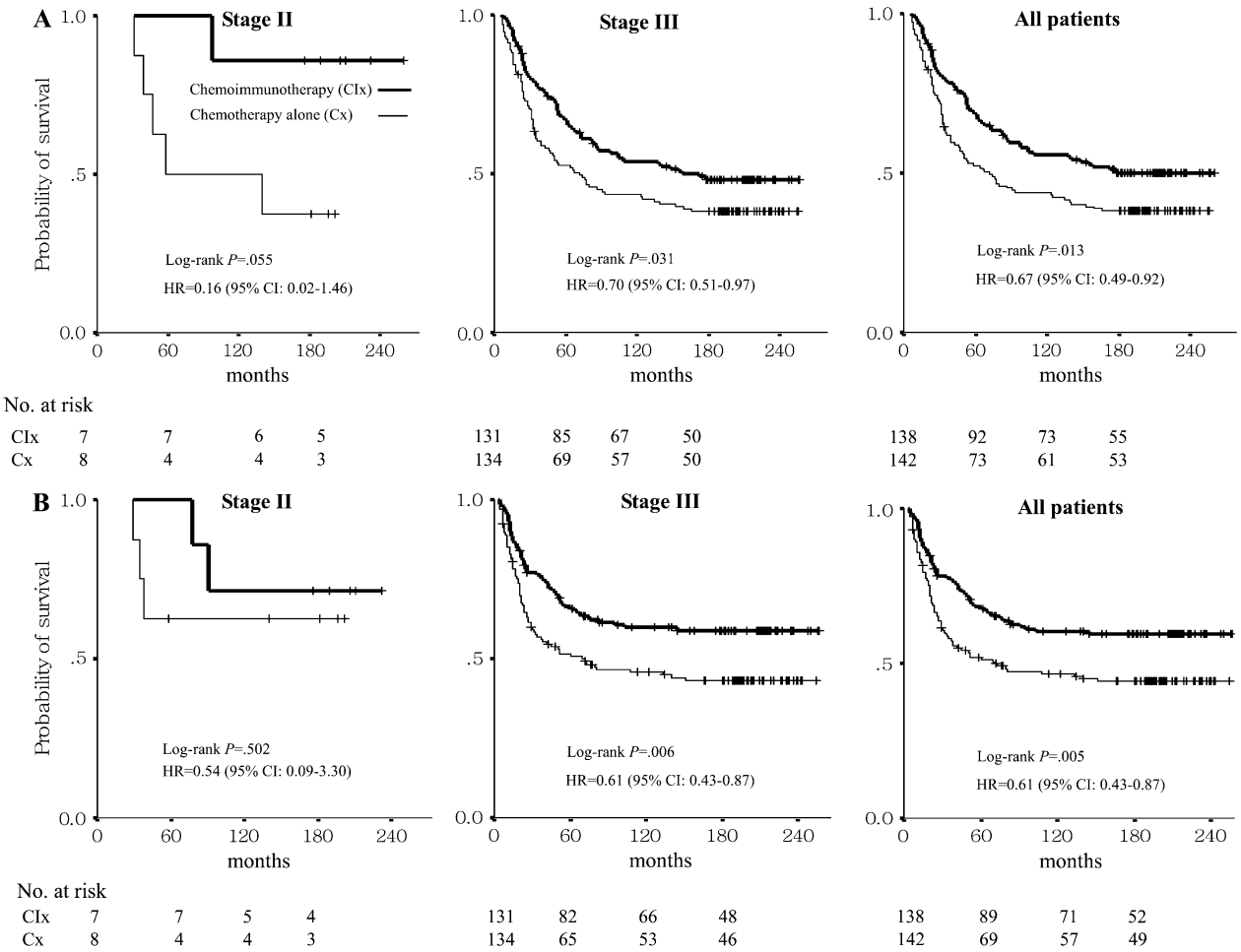

Figure 3. (A) Overall survival and (B) recurrence-free survival based on the American Joint Cancer Committee staging criteria (1983). HR, hazard ratio; CI, confidence interval; Cix, chemoimmunotherapy; Cx, chemotherapy.

Table 2. Subset analysis of survivals between the chemotherapy (A) and chemoimmunotherapy (B) arms according to AJCC staging (1983 and 2002)

	Patient number: arm A/B	Median OS (month) (95% CI)			Median RFS (month) (95% CI)		
		Arm A	Arm B	*P* value	Arm A	Arm B	*P* value
AJCC (1983)							
T stage							
T_2	38/40	152 (NA)	178 (NA)	0.879	NR	NR	0.614
T_3	12/19	31 (11–51)	NR	0.011	29 (9–49)	NR	0.022
T_{4a}	92/79	53 (20–86)	NR	0.029	50 (13–87)	NR	0.018
N stage							
N_0	29/31	NR	NR	0.414	NR	NR	0.914
N_1	74/66	91 (14–168)	NR	0.327	NR	NR	0.025
N_2	39/41	33 (28–38)	85 (0–186)	0.005	20 (11–29)	NR	0.036
Stage							
II	8/7	58 (0–187)	NR	0.055	NR	NR	0.502
III	134/131	72 (42–102)	158 (NA)	0.031	69 (0–146)	NR	0.006
AJCC (2002)							
T stage							
$T_{1–2}$	85/38	NR	NR	0.674	NR	NR	0.929
$T_{3–4}$	57/100	28 (20–36)	NR	<0.001	20 (14–26)	NR	<0.001
N stage							
N_0	28/31	166 (NA)	NR	0.381	NR	NR	0.937
N_1	71/59	159 (NA)	NR	0.083	NR	NR	0.033
N_2	30/29	32 (27–37)	85 (20–150)	0.014	20 (11–29)	NR	0.005
N_3	13/17	35 (12–58)	34 (0–68)	0.813	26 (13–39)	23 (12–34)	0.627
Stage							
IB	18/5	NR	NR	0.639	NR	NR	0.358
II	53/45	159 (NA)	NR	0.394	NR	NR	0.379
IIIA	47/51	39 (20–58)	NR	<0.001	26 (14–38)	NR	<0.001
IIIB	12/20	16 (4–28)	53 (0–110)	0.003	12 (4–20)	41 (NA)	0.007
IV	12/17	34 (2–66)	34 (0–68)	0.757	26 (11–41)	23 (12–34)	0.702

Gray areas are subgroups displaying significant survival advantages of chemoimmunotherapy over chemotherapy alone.
AJCC, American Joint Cancer Committee; OS, overall survival; CI, confidence interval; RFS, recurrence-free survival; NA, not assessable; NR, not reached.

four patients from the chemotherapy and chemoimmunotherapy arms, respectively. Grade 3/4 anemia was observed in three and one patients from each arm, respectively. There were no treatment-related deaths in either group (Table 3).

prognostic factors for survival

RFS and OS were analyzed according to age (<40 versus 40–59 versus ≥60 years), sex (male versus female), tumor location (antrum or pylorus versus body versus fundus or cardia versus diffuse), tumor differentiation (well versus moderately versus poorly differentiated or signet ring cell versus undifferentiated), type of surgery (subtotal versus total), and RDI of chemotherapy (below median versus above median). Bivariate analysis indicated significant survival differences ($P < 0.05$) according to the tumor differentiation and the RDIs of 5-FU and adriamycin (data not shown).

On multivariate analysis, the independent prognosticators for OS were tumor differentiation {$P = 0.001$; hazard ratio (HR) = 1.48 [95% confidence interval (CI) 1.18–1.86]} and treatment arm [$P = 0.016$; HR = 1.52 (95% CI 1.08–2.14)]. The independent prognosticators for RFS were tumor differentiation [$P < 0.001$; HR = 1.60 (95% CI 1.24–2.08)] and treatment arm [$P = 0.009$; HR = 1.66 (95% CI 1.33–2.42)].

Table 3. Incidences of severe (grade III/IV) toxicity by patients

Toxic effects	Chemotherapy		Chemoimmunotherapy	
	No. of patients		No. of patients	
	Total	Grade III/IV	Total	Grade III/IV
Alopecia	118	3	119	1
Nausea/vomiting	111	5	106	4
Diarrhea	46	8	40	4
Mucositis	57	3	62	3
Anemia	94	3	84	1
Leukopenia	105	3	104	4
Skin pigmentation	57	0	58	0
Infection	20	1	15	1
Fever	3	0	18	0

discussion

Compared with chemotherapy alone, the addition of the immunomodulator poly A:U to adjuvant FA chemotherapy prolonged RFS and OS in patients who had undergone curative D_2 gastrectomy. In terms of gastric cancer-specific survival, there was a greater survival benefit for chemoimmunotherapy arm. In patients receiving chemotherapy alone, the 5-year OS rates ranged widely from 31.0% to 95.7% as the tumor stage

increased from I_B to IVM_0. These survival rates are similar to those of other trials with Asian patients [16, 17]. The addition of poly A:U to standard chemotherapy reduced the risk of recurrence and cancer-related death by 16% at 5 years. The clinical relevance is evident from the fact that this risk reduction was maintained for 15 years after surgery. This is the first randomized trial to demonstrate a survival benefit of poly A:U as an adjuvant immunotherapy for gastric cancer which was maintained after long-term follow-up period.

The antitumor mechanism of poly A:U is complex. Researchers who successfully demonstrated an effect of adjuvant poly A:U in breast cancer suggested that one of the important mechanisms is tumor cell death through an activation of natural killer (NK) cells [18]. We also demonstrated that NK cell activity is enhanced after the administration of poly A:U [19]. This NK-boosting effect of poly A:U is mediated by interferon induction and lymphokine-activated killer cell activation [18]. Moreover, although chemotherapy is generally considered an immunosuppressant, in this study chemotherapy did not act as an immunosuppressant when combined with the immunomodulator, poly A:U. Paclitaxel enhances the antibody-dependent cell-mediated cytotoxicity of trastuzumab by a rapid recruitment of NK cells, the effect of which is twice as strong as trastuzumab alone [20]. These findings may reflect the strong synergistic effect of the combination of the drugs with different action mechanisms and indicate a rationale for chemobiotherapy or chemoimmunotherapy in designing future trials.

In reviewing the results of previous adjuvant studies, there were some factors identified that may have negatively affected the efficacy of adjuvant therapy on survival. First, since a large number of institutions have participated in adjuvant trials, there may be no standard surgical technique which is common across these institutions [21, 22]. Thus, the effects of adjuvant therapy cannot be compared adequately, considering that successful curative surgery is the single most important factor in prognosis. If patients with palliative resection were included in adjuvant trials, the efficacy of adjuvant therapy would thus be likely underestimated. Because limited lymphadenectomies increase the chance of residual tumor after the resection, D_2 or D_3 resection has been carried out as a standard curative surgery in Asia, especially in Korea and Japan. For this reason, we also carried out standardized D_2 or D_3 resection in this study. Secondly, the eligibility criteria of earlier adjuvant trials also included heterogeneous categories of pathological stages ranging from stage I to stage IV disease (N_3 or T_{4b}) [21–23]. In earlier Asian trials, subset analyses indicated that the survival benefit was greatest in stage II and III patients or in stage III patients [24, 25]. On the basis of these results, we excluded the early- (T_1) and advanced-stage (T_{4b}, N_3) cancer. We think proper patient selection and standardized extended surgery may have contributed to the illustration of efficacy of adjuvant chemoimmunotherapy in this trial.

Most Western studies on adjuvant chemotherapy for gastric cancer have reported negative results, whereas Asian trials have tended to favor adjuvant chemotherapy [3, 4]. In the 1980s, Korean and Japanese researchers were so convinced that adjuvant chemotherapy improved survival in gastric cancer, especially for extended lymphadenectomized patients, and that a randomized trial comparing adjuvant therapy versus surgery alone was considered unethical. Therefore, we designed this trial comparing chemoimmunotherapy versus chemotherapy. In a recent randomized phase III trial of stage II/III gastric cancer patients, adjuvant S-1 monotherapy gave a survival benefit over surgery alone after D_2 gastrectomy [26]. For advanced gastric cancer, S-1 plus cisplatin was superior to S-1 monotherapy [27]. On the basis of these results, we are considering switching the adjuvant trial regimen to an S-1-based regimen.

Here, we did not stratify patients according to the T or N status. Therefore, there were more T_{4a} patients and fewer T_2 patients in the chemotherapy group compared with chemoimmunotherapy group. These differences, however, were not statistically significant. Differences in the distribution of potential prognosticators between the two treatment arms were observed only for surgery type, not for age, sex ratio, tumor location, or tumor differentiation. Some studies have reported survival benefits of adjuvant chemotherapy in selected subgroups with node-positive $T_2/T_3/T_4$ or stage III tumors [22, 23, 28]. In our study, the subset analyses according to tumor depth (T) and lymph node involvement (N) were also similar; survival benefits of chemoimmunotherapy over chemotherapy alone were observed in moderately advanced stages such as T_3/T_{4a}, N_2, or stage III. Also, the N_1 patients receiving chemoimmunotherapy showed a borderline survival benefit. Several adjuvant chemoimmunotherapy trials using other immunomodulators for gastric cancer also showed survival benefit over chemotherapy alone in patients with pT_2/T_3 or stage III tumors.[29, 30] These data indicate that stage-oriented adjuvant chemotherapy or chemoimmunotherapy regimens may be imperative in the future.

Chemoimmunotherapy was well tolerated in general. Immunotherapy did not disturb the administration of chemotherapy. As a result, a similar number of patients completed chemotherapy in both arms (66.9% versus 68.8%). Also, no major differences in toxicity were noted between the two treatment arms. Long-term cardiac events were evaluated in this study. Four patients died from heart disease; two of these from myocardial infarction (29, 155 months), one from arrhythmia (109 months), and one from CHF (109 months). Some patients receiving 100 mg of poly A:U in 20 ml saline exhibited a temporary fever (<38°C) lasting several hours. In later studies, however, fever was rarely observed when the same dosage of the poly A:U was administered in 50 ml instead of 20 ml of saline.

To conclude, in resectable gastric cancer, adjuvant chemoimmunotherapy with FA and poly A:U conferred a survival benefit over chemotherapy alone during a 15-year follow-up. Chemoimmunotherapy was found to be as tolerable as chemotherapy alone.

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