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ORIGINAL ARTICLE

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Dose intensity of uracil and tegafur in postoperative chemotherapy for patients with poorly differentiated gastric cancer

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Abstract A retrospective analysis of postoperative chemotherapy had shown the continuous administration of UFT, an oral preparation of 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) and uracil at a molar ratio of 1:4, to be effective for poorly differentiated gastric cancer. We therefore sought to determine prospectively the effective dose of postoperative chemotherapy with UFT for patients with poorly differentiated gastric cancer following a curative resection. We determined the effect of the combined intravenous administration of mitomycin C (MMC) and oral treatment with protein-bound polysaccharide Kreha (PSK), extracted from the basidiomycete *Coriolus versicolor*, and UFT at a dose of either 8 mg/kg or 12 mg/kg daily for 1 year. A total of 224 patients with poorly differentiated stage II–IV gastric cancer were entered into this study after undergoing a curative resection. No differences were observed between the two treatment groups in terms of prognostic factors, the toxicity rate or the doses of the drugs prescribed, other than UFT. The higher dose of UFT in maintenance therapy led to a decrease in the recurrence rate ($P < 0.05$), and increases in disease-free survival and cause-specific survival ($P < 0.05$). UFT at 12 mg/ kg in postoperative chemotherapy was thus found- to improve the postoperative results with no increase in toxicity for poorly differentiated gastric cancer, and is also cost-effective for outpatients.

Key words Gastric cancer · Postoperative chemotherapy · UFT · Recurrence · Prognosis

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Introduction

Fluorinated pyrimidines, combined with or without other anticancer drugs, have been prescribed for patients undergoing resection for gastric cancer [12, 19]. Postoperative adjuvant chemotherapy with 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) has been shown to improve the survival of patients with stage III gastric cancer [2]. Maehara et al. [16] found that the combination of mitomycin C (MMC) and UFT (tegafur and uracil at a molar ratio of 1:4), compared with MMC and tegafur, lengthens the survival time of patients with stage IV gastric cancer by approximately twofold. Thus, UFT, developed by Fujii et al. [4], has been widely prescribed for a variety of solid tumors including gastric cancer [16, 21, 22, 26]. Uracil augments the cytotoxicity of tegafur by inhibiting the degradation of 5-fluorouracil (5-FU) [8]. Using an in vivo chemosensitivity test, UFT has been found to be more effective than 5-FU and its analogues for treating patients with gastric cancer [15]. In addition, clinical trials have also revealed higher levels of 5-FU in both the blood and tumor tissue in patients treated with UFT, in comparison with those treated with tegafur [7]. In the United States, a phase II trial of the combination of UFT and leucovorin revealed a 42.2% response rate for colorectal cancers [22].

A retrospective analysis of the combination of MMC and UFT has shown this protocol to be effective in patients with poorly differentiated gastric cancer [16]. Arima et al. [1] also reported that the combined administration of MMC and UFT increases the survival time of patients with poorly differentiated gastric cancer

following curative resection, compared with a protocol comprising MMC and tegafur. It was thus speculated that the greater increases in the 5-FU levels in the blood and tumor tissue following administration of UFT than of tegafur could possibly lead to a more effective treatment of poorly differentiated gastric cancer.

We therefore conducted a prospective study of a chemotherapy protocol for poorly differentiated gastric cancer. To determine the effective dose we used continuous administration of UFT at 8 mg/kg and 12 mg/kg. Protein-bound polysaccharide (Kreha, PSK) has been reported to be effective in postoperative treatment as an immunomodulator when combined with fluorinated pyrimidines in patients with gastric cancer [17, 19]. We therefore used this drug in both groups.

Patients and methods

Patients and treatments

Patient eligibility was determined on the basis of: (1) a histological diagnosis of poorly differentiated gastric cancer by preoperative biopsy; (2) a macroscopic diagnosis of a curative resection and stage II–IV, on completion of all surgical procedures; (3) an age of less than 76 years; (4) a performance status using the Eastern Cooperative Oncology Group (ECOG) criteria [20] of grade 0–2; (5) no second, previous or concurrent primary malignancies in any other organs; (6) an adequate organ system function (leukocytes $>4000\ mm^{-3}$, platelets $>100\ 000\ mm^{-3}$, AST and ALT <100 U). The patients were prospectively randomized immediately after operation to either group A or group B.

A total of 224 patients were entered into this study between July 1986 and June 1988. The protocol (Fig. 1) was as follows. The inductive regimen for group A comprised an intravenous (i.v.) injection of 20 mg MMC on the day of operation followed by 10 mg i.v. on postoperative day 1 [18]. As maintenance therapy, group A received UFT (Taiho Pharmaceutical Co., Japan) orally at a daily dose of 8 mg/kg (in terms of tegafur) and PSK (Kreha Chemical Industry Co., Japan) orally at a daily dose of 3 g beginning 2 weeks after the operation for 1 year.

PSK is a protein-bound polysaccharide preparation extracted from the basidiomycete *Coriolus versicolor* [19, 25]. This compound contains about 15% protein and its average relative molecular mass is approximately 1×10^5. The sugar portion consists of five kinds of sugar, mainly glucose, while the major protein has a straight-chain structure with (β1-4)-glucan branching at position 6 or 3. The protein has 19 amino acids, mainly consisting of aspartic acid, glutamic acid, and leucine.

The regimen for group B utilized a UFT dose of 12 mg/kg (in terms of tegafur) daily, with the same protocol for MMC and PSK as the group A regimen. The pathological diagnosis and classifications were evaluated according to the General Rules for Gastric Cancer Study in Surgery and Pathology used in Japan [9]. The World Health Organization (WHO) criteria were used to define the toxicity of the postoperative chemotherapy [27].

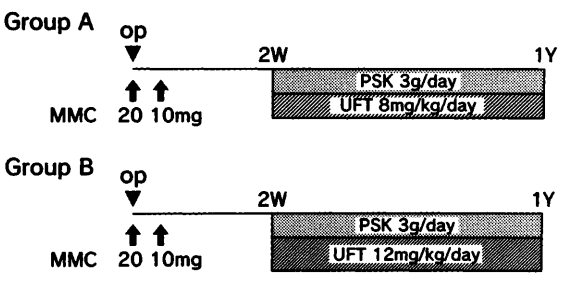

Fig. 1 Schedule for the administration of chemotherapy

After surgery, the patients were entered into a regular follow-up program. Blood protein, albumin, white blood cells, red blood cells, platelets, hemoglobin, hematocrit, transaminases, blood urea nitrogen and creatinine were examined every 2 weeks for the first year and then at intervals of 3 to 6 months for 5 years. Roentgenography of the gastrointestinal tract, endoscopic procedures, computed tomography, and ultrasonography were carried out at 6-month intervals for the first year and then at 1-year intervals for 5 years.

Statistical analysis

The effects of this chemotherapy were assessed in terms of cause-specific survival, disease-free survival and recurrence rates. The BMDP Statistical Package Program (BMDP, Los Angeles, Calif.) for the IBM 3090 (IBM Corporation, Armonk, N.Y.) mainframe computer was used for all analyses [3]. The BMDP P4F and P3S programs were used for the Chi-squared test and the Mann-Whitney test to compare the data between the patient groups. The BMDP P1L program was used to analyze the survival time by the Kaplan-Meier method, and the Mantel-Cox test was used to test for the equality of the survival curves. The level of significance was taken as $P < 0.05$.

Results

Of the 224 patients entered, 28 (12.5%) were ineligible: 1 had no gastric cancer, 3 had double cancers, 1 had been previously treated by chemotherapy, 1 was over 76 years of age at operation, and 22 had macroscopic stage I gastric cancer. No difference was found between the groups in terms of excluded patients.

Clinicopathological features

The clinicopathological details of the 196 eligible patients (100 in group A, 96 in group B) are shown in Table 1. There were no significant differences between groups A and B with regard to sex, age, tumor stage, serosal invasion or lymph node metastasis, nor with regard to surgical procedure (gastric resection and lymph node dissection).

Doses of drugs

There were no differences in the dosages of MMC and PSK between the groups (Table 2). The UFT dosage was higher in group B than in group A ($P < 0.05$).

Survival rates

The data of patients who died from causes other than gastric cancer were considered as censored in the statistical analysis. A complete follow-up was available either up to death or until 5 years.

Table 1 Comparison of the clinicopathological characteristics between the patients in groups A and B. There were no significant differences between the two groups

Factor	Category	Group A ($n = 100$)	Group B ($n = 96$)
Sex	Male	55	54
	Female	45	42
Age (years)		56.1 ± 11.7	56.0 ± 11.9
Macroscopic stage	II	23	35
	III	67	56
	IV	10	5
Serosal invasion	S0	18	15
	S1	20	27
	S2	56	50
	S3	5	3
	Unknown [a]	1	1
Histological depth of invasion	No serosal invasion	56	50
	With serosal invasion	43	43
	Unknown [a]	1	3
Macroscopic lymph node metastasis	No	16	15
	Yes	84	81
	Unknown [a]	0	0
Histological lymph node metastasis	No	34	33
	Yes	65	60
	Unknown [a]	1	3
Lymph node dissection	R1	2	2
	R2	76	76
	R3	21	18
	Unknown [a]	1	0
Gastrectomy	Total	46	56
	Partial	54	39
	Unknown [a]	0	1
Histological curability	Curative	92	91
	Noncurative	8	5

[a] All unknown cases were excluded from the statistical analysis

Figure 2 shows the cause-specific survival curves of groups A and B among the eligible patients. A significant difference was observed between the survival curves ($P < 0.05$). The 5-year survival rate was 58.6% for group A and 69.4% for group B. Of the 196 eligible patients, 13 were excluded from the analyses of the cause-specific survival rate, disease-free survival rate and recurrence, because of a histologically noncurative resection. Therefore, 183 patients who received a histologically curative resection were finally used for the analyses. Figure 3(a) shows the cause-specific survival curves of groups A and B among the patients with a histologically curative resection. A significant difference was also seen between the survival curves ($P < 0.05$). The 5-year survival rate was 59.4% for group A and

Table 2 Drug dosages. Values are mean ± SD, with ranges shown in parentheses

Drug	Group A ($n = 100$)	Group B ($n = 96$)
MMC (mg)	25.2 ± 8.4 (10–50)	26.2 ± 8.5 (10–72)
UFT (g)	107.2 ± 87.3 (38.7–397.6)	141.9 ± 123.4* (45.9–651.6)
PSK (g)	745.7 ± 637.1 (207–2982)	800.4 ± 708.9 (203–3258)

*$P < 0.05$

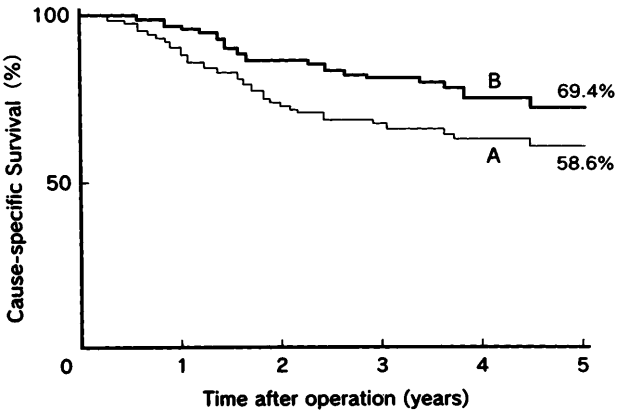

Fig. 2 The cause-specific survival curves for the patients in groups A and B with poorly differentiated gastric cancer. There were 100 patients in group A and 96 patients in group B. A significant improvement in the survival time was noted in the group B patients in comparison with group A patients ($P < 0.05$)

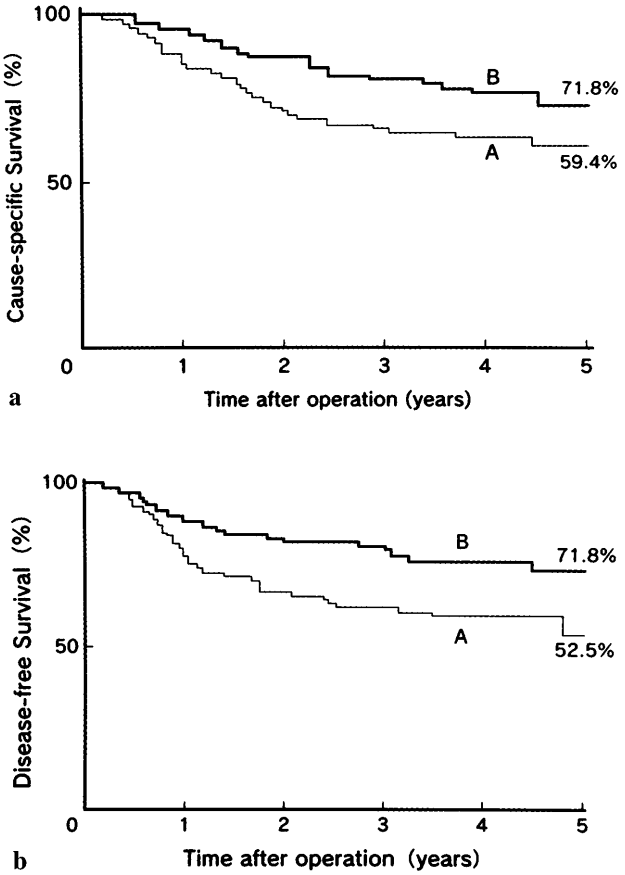

Fig. 3a,b The cause-specific survival (**a**) and disease-free survival (**b**) for patients who had undergone a histologically curative resection. There were 92 patients in group A and 91 patients in group B. Significantly better cause-specific survival time (**a**) and disease-free survival time (**b**) were noted in group B patients than in group A patients ($P < 0.05$)

71.8% for group B. Figure 3(b) shows the disease-free survival curves for both groups. A significantly higher disease-free survival time was noted in group B than in group A ($P < 0.05$). The 5-year survival rate was 52.5% for group A and 71.8% for group B.

Recurrence pattern

The result in the patients who underwent a curative resection were examined histologically for the rate and site

Table 3 Recurrence after histological curative resection for gastric cancer

	Group A ($n = 92$)	Group B ($n = 91$)	*P*-value
Without recurrence	55	70	< 0.05
With recurrence	37	21	
Peritoneum	25	13	
Hematogenous	6	7	
Local	6	3	
Lymph node	7	1	
Others	1	2	

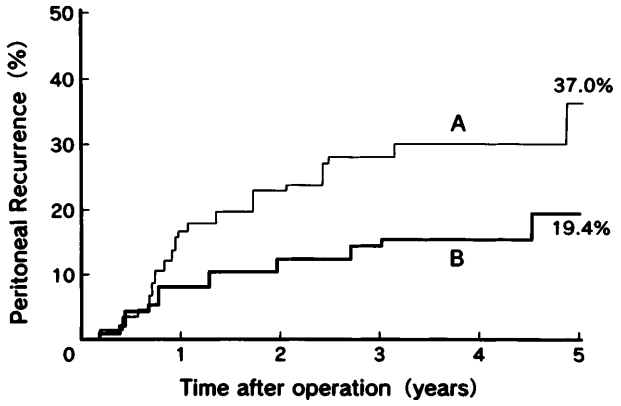

Fig. 4 The cumulative frequency of isolated peritoneal recurrence as the first event. A significant difference was observed between groups A and B ($P < 0.05$)

of recurrence, as shown in Table 3. The rate of recurrence was less in group B than in group A ($P < 0.05$). In particular, the rate of peritoneal recurrence was lower and the estimated cumulative frequency of isolated peritoneal recurrence at 5 years was 37.0% in group A and 19.4% in group B ($P < 0.05$; Fig. 4).

Toxicity

Table 4 summarizes the factors related to grade III or IV toxicity, according to the WHO criteria. Various side effects also occurred in each group, as did hematologic toxicities. However, no differences were observed between the treatment groups.

Discussion

A retrospective analysis of the effectiveness of MMC and UFT compared with MMC and tegafur has been previously reported for poorly differentiated gastric cancer [16]. There have been reports on the difference of response to chemotherapy between well and poorly differentiated gastric cancer cells [14, 24]. Konishi et al. [11] reported that sequential chemotherapy with methotrexate and 5-FU is effective for poorly differentiated

Table 4 Toxicities. Values are percentage of patients fulfilling each criterion for grade III of IV toxicity according to WHO criteria

Toxicity	Group A ($n = 100$)	Group B ($n = 96$)
Leukopenia (< 3000 cells mm^{-3})	17.0	13.5
Anaemia (hemoglobin < 9.5 g/dl)	7.0	4.2
Thrombocytopenia (< 70 000 cells mm^{-3})	4.0	3.1
Liver dysfunction (GOT > 100 U)	5.0	7.3
Anorexia	10.0	13.5
Nausea, vomiting	10.0	11.5
Diarrhea	7.0	3.1
Skin pigmentation	6.0	4.2

gastric cancer, but not for well-differentiated cancer. The higher activity of *de novo* pyrimidine nucleotide synthesis is considered to play a role in the effectiveness of 5-FU in poorly differentiated gastric cancer [10, 23].

As the effectiveness of postoperative chemotherapy depends on the type of gastric cancers, the character of the tumor must be carefully determined before the optimal chemotherapeutic regimen can be determined for each individual patient. The protocol consisting of an early administration of MMC and the continuous administration of a fluorinated pyrimidine has been widely prescribed in Japan. Maehara et al. [17] have reported that the postoperative adjuvant chemotherapy of MMC, tegafur and PSK increases the survival time for gastric cancer compared with no chemotherapy. Lise et al. [13] and Hallissey et al. [6] have reported that adjuvant chemotherapy with the combination 5-FU, doxrubicin and MMC (FAM) is highly toxic and cannot be advocated as standard adjuvant treatment for gastric cancer. Therefore, a less toxic and more active regimen is required for gastric cancer.

In this study, the effectiveness of different doses of UFT was examined in the treatment of poorly differentiated gastric cancer patients who had undergone curative resection. The cytotoxicity of 5-FU is dose- and time-dependent and the oral administration of UFT tends to lead to an accumulation of 5-FU in the blood [7]. In addition, poorly differentiated cancer has been found to be more sensitive to 5-FU [14]. Therefore, increasing the dose of UFT from 8 mg/kg to 12 mg/kg may improve the effectiveness of postoperative chemotherapy as a result of the increased levels of 5-FU in both the blood and the tumor tissue. In cases of advanced colorectal cancer, a clear relationship between 5-FU plasma levels, toxicity and efficacy has been noted at any i.v. dose of 5-FU with leucovorin [5]. The treatment regimen with the higher UFT dose led to a significantly lower incidence of recurrence, in particular for patients with peritoneal dissemination. Increasing the dose of UFT is therefore thought to be essential for reducing the peritoneal recurrence of gastric cancer. The toxicity of the higher dose of UTF was not greater than the lower dose and was lower than the toxicity of the FAM regimen [13]. The patients seemed to tolerate the higher UFT dose as well as they did the lower dose.

Our findings suggest that postoperative continuous chemotherapy with UFT at the increased dose of 12 mg/kg appears to be a viable approach for both reducing the recurrence rate and for curing patients with poorly differentiated gastric cancer, with no increased toxicity. As the oral form of UFT can also be prescribed for outpatients, this protocol is also cost-effective for postoperative chemotherapy.

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