Cancer Chemother Pharmacol (1998) 42 (Suppl): S80–S84

ORIGINAL ARTICLE

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Clinical trials for advanced gastrointestinal cancers in Japan

Abstract No standard chemotherapy regimen for the treatment of advanced gastrointestinal cancer exists. However, 5-fluorouracil (5-FU) is being used more frequently as a key component of combination therapy regimens for this disease, and including cisplatin (CDDP) in combination therapy regimens produces significant tumor shrinkage. Although oral formulations of 5-FU are widely used in Japan, their clinical activity and toxicity have not been thoroughly evaluated. In 1992, the Japan Clinical Oncology Group initiated a phase III study in which the survival rates of patients treated with 5-FU 800 mg/m^2/day for 5 days by continuous infusion (5-FUci), 5-FUci with CDDP 20 mg/m^2/day for 5 days by infusion, or oral uracil/Ftorafur 375 mg/m^2/day with weekly MMC 5 mg/m^2 iv were compared. This study was closed with 280 patients accrued in 1997, and final analysis was made in early 1998. Irinotecan and paclitaxel are new drugs with activity against gastric cancer. Combination chemotherapy consisting of irinotecan with CDDP has also been evaluated. For treatment of metastatic colorectal cancer, the only active drug previously available in Japan was 5-FU, although 5-FU + leucovorin is the international standard regimen. Irinotecan is now approved in Japan, Europe, and the USA and is the most effective drug for 5-FU-refractory patients. The optimal irinotecan and 5-FU combination regimen is being extensively examined but further trials aimed at accumulating basic data are warranted.

Key words Clinical trial · Gastrointestinal cancer

Work presented at the 13th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "Strategic Cross Talk between Major Oncology Groups/Clinical Pharmacology in Cancer Chemotherapy", 17–18 October 1997, Nagoya, Japan

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Introduction

Gastric and colorectal cancer are common gastrointestinal cancers in Japan [5]. Early diagnosis using the double-contrast radiographic method and skillful surgical resection have contributed to improving the 5-year survival of patients with these cancers. However, in advanced or metastatic disease, treatment outcome remains poor. Any breakthrough in the treatment of this condition will require well-designed clinical trails. The Japan Clinical Oncology Group (JCOG) trials and some investigational drug trials that have been conducted in Japan are reviewed and discussed in this paper.

JCOG

JCOG was founded in 1978 by Dr Keiichi Suemasu, former director of the National Cancer Center. Supported by a grant from the Japanese Ministry of Health and Welfare, the aim of the group is to conduct clinical research in cancer patients. In the mid-1980s, Dr Masanori Shimoyama, present chief investigator of JCOG, reorganized the JCOG clinical trials system and trials became more functional.

Three central divisions are under the direction of the chief investigator: a data center; a clinical trial review committee; and a monitoring committee. JCOG has nine disease-specific study groups in the areas of lung, gastric, esophageal, and breast cancer, lymphoma, bone marrow transplantation, and gynecologic malignancies. Recent annual patient accrual exceeds 1000.

Gastric cancer

Incidence of gastric cancer

Gastric cancer is the most common cancer in Japan, with recent statistics showing that approximately 50,000 patients

Table 1 Mortality due to malignant neoplasms in Japan (1995)

Neoplasm	No. of deaths (%)
Digestive organs	153,035 (58.18)
Esophagus	8,638 (3.28)
Stomach	50,076 (19.04)
Colon	20,286 (7.71)
Rectum	10,869 (4.13)
Liver	31,707 (12.05)
Pancreas	16,019 (6.09)
Lung	45,723 (17.38)
Breast	7,819 (2.97)
Prostate	5,399 (2.05)
Leukemia and lymphoma	15,479 (5.89)
Total	263,022 (100.00)

Table 2 Gastric cancer survival rates (%) by clinical stage in National Cancer Center hospitals (1985–1995)

Stage	No. of patients	Survival rate (%)		
		One year	3 years	5 years
I	1111	97.5	94.3	91.6
II	179	91.3	79.2	77.1
III	279	84.2	57.5	46.1
IV	352	49.7	15.6	8.3
Total	1921	84.9	71.8	67.2

Table 3 JCOG Gastrointestinal Oncology Study Group protocols (*CDDP* cisplatin, *5′DFUR* doxifluoridine, *FT* tegafur, *5-FU* 5-fluorouracil, *MMC* mitomycin C, *MTX* methotrexate, *UFT* uracil/tegafur)

Year	Phase (trial number)	Protocol
1984–1992	Randomized II	UFT + MMC vs. FT + MMC
	II	5′DFUR + CDDP
	II	Etoposide + doxorubicin + CDDP
	II	5-FU + CDDP as second-line therapy
	II	5-FU + CDDP as first-line therapy
1992–	III (JCOG 9205)	5-FU vs. 5-FU + CDDP vs. UFT + MMC
	II (JCOG 9207)	MTX + 5-FU as second-line therapy
	II (JCOG 9410)	5′DFUR in the elderly
	II (JCOG 9603)	MTX + F-FU in ascites

Table 4 Phase II results from JCOG (*EAP* etoposide + doxorubicin + cisplatin, *FP* 5-fluorouracil + cisplatin, *5′FP* doxifluridine + cisplatin, *FTM* tegafur + mitomycin C, *UFTM* uracil/tegafur + mitomycin C)

Chemotherapy regimen	No. of patients	Response rate (%)	Two-year survival (%)	Mean survival duration (days)
FTM	50	8	4	183
UFTM	39	21	3	252
5′FP	49	29	14	243
EAP	42	52	14	273
FP	46	39	9	225
Total	226	29	9	228

die of it annually [5], accounting for 19% of all cancer deaths in Japan in 1995 (Table 1). Cancers of the digestive organs accounted for approximately 60% of all cancer deaths.

Outcomes of surgical resection in Japan

The best treatment strategy for gastric cancer is surgical resection of primary tumors by specialist surgeons. Survival rates for gastric cancer patients who underwent resection at the National Cancer Center Hospital, Tokyo, are shown in Table 2 [5]. Most patients with early-stage disease survive >5 years with curative surgery; however, the 5-year survival rate among patients with stage IV gastric cancer is <10 %. Prognosis is particularly poor for patients with distant metastases at presentation and the number of patients in whom effective systemic chemotherapy would be useful is large.

JCOG Gastrointestinal Oncology Study Group

Clinical trials for gastrointestinal cancers are conducted by the JCOG Gastrointestinal Oncology Study Group. Although the primary target tumor type was initially gastric cancer, recently the group's scope has expanded to include chemotherapy for metastatic esophageal and colorectal cancers. Under its chairmen, Professor Minoru Kurihara, Showa University, Tokyo, and Dr Shigeaki Yoshida, National Cancer Center Hospital East, Kashiwa, the Gastrointestinal Oncology Study Group is working to determine the standard chemotherapy for patients with advanced gastrointestinal cancers. The protocols studied are shown in Table 3.

The first trial evaluated oral regimens and showed that uracil/tegafur (UFT) plus mitomycin C (MMC) produces better response rates than tegafur (FT) plus MMC. The subsequent four phase II studies were conducted to evaluate the efficacy and toxicity of cisplatin (CDDP)-containing regimens. Of the three regimens studied, 5-fluorouracil (5-FU) plus CDDP remained as a candidate for the investigational arm of the randomized phase III trial. This study (JCOG 9205) was started in 1992. The other three regimens studied included biochemical modulation chemotherapy and the evaluation of clinical benefit in special target groups including the elderly and patients with severe ascites. The results of five of the phase II studies conducted to date are summarized in Table 4 [9, 13].

Before the introduction of CDDP-containing regimens, response rates were not high. The introduction of CDDP produced higher response rates of 30–50%. However, although tumor shrinkage occurred, median survival duration ranged from 7 to 9 months. The primary question to be answered is what is the survival benefit of these regimens.

Before the phase III study was initiated, the results of four randomized clinical trials in advanced gastric cancer were reported (Table 5) [4, 7, 8, 20]. The conclusion of these studies, two of which had 5-FU as a control arm, was that there was no significant difference in survival between treatment arms. In the 5-FU control arms, survival duration was 7.5 months and 6.1 months, respectively. Recently, the European Organization for Research and Treatment of

Table 5 Prospective randomized trials of combination chemotherapy in advanced gastric cancer (*EAP* etoposide + doxorubicin + cisplatin, *ELF* etoposide + leucovorin + 5-fluorouracil, *EORTC* European Organization for Research and Treatment of Cancer, *FAM* 5-fluorouracil + doxorubicin + mitomycin C, *FAMe* 5-fluorouracil + doxorubicin + methyl-CCNU, *FAMTX* 5-fluorouracil + doxorubicin + methotrexate, *FAMe-TZT* 5-fluorouracil + doxorubicin + methyl-CCNU + triazinate, *FAP* 5-fluorouracil + doxorubicin + cisplatin, *FP* 5-fluorouracil + cisplatin, *5-FU* 5-fluorouracil, *MSKCC* Memorial Sloan-Kettering Cancer Center, *NCCTG* North Central Cancer Treatment Group, *PELF* cisplatin + epirubicin + leucovorin + 5-fluorouracil)

Group	Regimen	No. of patients	Response rate (%)	Survival rate (%)	*P*
EORTC (1991)	FAMTX	105	41	10.5	0.004
	FAM	103	9	7.2	
MSKCC (1992)	FAMTX	30	33	7.3	NS
	EAP	30	20	6.1	
Korea (1993)	FP	103	51	9	NS
	FAM	98	25	7	
	5-FU	94	26	7.5	
NCCTG (1994)	FAMe-TZT	79		7.7	NS
	FAMe	53		6.1	
	FAP	51			
	5-FU	69		6.1	
EORTC (1995)	FAMTX	92	25	7	NS
	FP	96	30	8	
	ELF	93	17	8	
Italian Oncology Group for Clinical Research (1994)	FAM	52	15	5.6	NS
	PELF	85	43	8.1	

Table 6 JCOG 9205: 3-arm randomized clinical trial in gastric cancer (*5-FU* 5-fluorouracil, *MMC* mitomycin C, *UFT* uracil/tegafur)

Arm	Schedule
5-FUci	5-FU 800 mg/m^2/day by continuous infusion on days 1–5, every 4 weeks
FP	5-FU 800 mg/m^2/day by continuous infusion on days 1–5 + cisplatin 20 mg/m^2/day iv on days 1–5 every 4 weeks
UFTM	UFT 375 mg/m^2/day po, daily + MMC 5 mg/m^2 iv weekly

Table 7 Phase II irinotecan study in gastric cancer (*CDDP* cisplatin, *CPT-11* irinotecan)

Treatment	No. of patients	Response rate (%)
CPT-11	76	18.4
CPT-11 + CDDP	24	41.7
CPT-11 + CDDP	44	47.7
No prior chemotherapy	29	58.6
Prior chemotherapy	15	26.7

Cancer (EORTC) and an Italian group reported the results of their phase III studies [3, 19] showing that survival duration, at 7 months and 8 months, respectively, was not improved.

The protocol used in JCOG 9205 was designed based on these results. 5-FU alone was selected as the control, and 5FU plus CDDP and UFT plus MMC as the investigational arms. Drug doses and administration schedules are summarized in Table 6. The primary endpoint of the trial is survival.

Promising new regimens in gastric cancer

Despite vigorous efforts, progress in cancer therapy is slow. In an attempt to improve this situation, two ways of developing new treatments can be employed. The JCOG study is directed mainly at evaluating combination therapy involving approved anticancer drugs in phase II or III studies. However, clinical studies contracted by pharmaceutical companies are also undertaken and are directed toward evaluating investigational new drugs in phase I or II studies. Thus the clinical development of irinotecan and paclitaxel were conducted outside the JCOG program.

Irinotecan was originally semisynthesized and clinically evaluated in Japan. In our phase II study, which included patients who had received prior chemotherapy, an 18.4% response rate was obtained (Table 7) [6].

The National Cancer Center Hospital and National Cancer Center Hospital East also conducted a phase I study of irinotecan in combination with CDDP because these drugs had a synergistic effect in vitro and in vivo and this regimen was reported to be active in lung cancer [11, 12]. In this study, a response rate of 41.7% was obtained [18]. Thus a phase II study of this protocol was immediately started as a collaborative effort between six hospitals. A similar response rate of 47.7% overall and 58.6% in patients who had received no prior chemotherapy was obtained [2]. Based on these data, a phase III study of this combination is planned for 1998.

The use of paclitaxel in gastric cancer has also been studied. Ohtsu et al. reported a response rate of 21.4% in 14 second-line patients treated with paclitaxel 210 mg/m^2 as a 3-h infusion [14]. At the same time, Ajani et al. published comparable results [1]. Thus paclitaxel is moderately active in gastric cancer (Table 8). A phase II study of the same dose and infusion schedule as used in the study by Ohtsu et al. is ongoing in Japan; modified, short-term premedication was used in this study.

Table 8 Phase II paclitaxel study in gastric cancer

Study	Paclitaxel dose (mg/m²)	No. of patients	Response rate (%)
Japan [12] (second line)	210/3 h	14	21.4
USA [1] (first line)	200/3 h	13	8
	200/24 h	17	23

Table 9 Colon and rectal cancer survival rates (%) by clinical stage in National Cancer Center hospitals (1985–1995)

Dukes' stage	No. of patients	Survival rate (%)		
		One year	3 years	5 years
Colon cancer				
A	180	98.3	96.5	92.8
B	257	97.3	93.4	88.8
C	268	95.1	82.9	76.1
D	191	56.0	19.5	14.8
Total	904	87.8	74.6	69.5
Rectal cancer				
A	167	97.6	95.0	94.1
B	182	94.5	88.6	81.1
C	265	94.6	76.7	65.4
D	121	63.0	23.9	13.6
Total	735	90.1	75.3	67.5

The above data indicate that JCOG has contributed to the improvement of the quality of clinical trials in gastrointestinal cancer in Japan.

Colorectal cancer

Incidence and results of surgical resection

Deaths in Japan due to colorectal cancer exceeded 30,000 in 1995 (Table 9) [5]. The 5-year survival rates of Dukes' C stage disease were 76% in colon and 65% in rectal cancer patients. In Dukes' D disease, 5-year survival rates were $<15\%$.

Chemotherapy for metastatic colorectal cancer in Japan

Despite progress in chemotherapy, only one drug active in colorectal cancer has been available over the past 40 years: 5-FU. Many clinical trials have attempted to identify drugs with novel activity in this disease, and in Japanese trials oral fluoropyrimidines were evaluated for many years. FT, UFT, doxifluoridine, and other fluoropyrimidine derivatives were approved based on limited clinical data. Recently, UFT was reevaluated in a well-designed trial conducted outside Japan [15]. However, in Japan metastatic colorectal cancer patients are treated surgically and therefore patient accrual to chemotherapy trials is slow, making it difficult to obtain good data.

Until recently, JCOG had not conducted colorectal cancer trials, but a phase II study of sequential irinotecan and infusion 5-FU was recently conducted by two National Cancer Center hospitals. This strategy proved to be one of the success stories of the JCOG system (Table 10) [16, 17, 21]. The first combination schedule studied involved 5-FU and irinotecan administered simultaneously. However, the response rate was only 11%, although two-thirds of the patients had received prior chemotherapy. The administration schedule was modified to a sequential one and the objective response rate increased to 32%. A phase II study of this sequential schedule was initiated in 1998.

Table 10 Phase II irinotecan study in colorectal cancer (*CPT-11* irinotecan, *5-FU* 5-fluorouracil)

Treatment	No. of patients	Response rate (%)
CPT-11	63	27.0
No prior chemotherapy	12	33.3
CPT-11 + 5-FU		
Simultaneous	36	11.1
No prior chemotherapy	12	16.7
Sequential	25	32.0

Conclusions

Gastrointestinal cancer is common in Japan. The JCOG Gastrointestinal Oncology Study Group has contributed to improving the quality of clinical trials in this area and has obtained some valuable results. Irinotecan and other new anticancer drugs of Japanese origin may become integral parts of cancer chemotherapy regimens in the near future. JCOG should collaborate with non-Japanese clinical trial groups to improve the treatment of specific types of cancer.

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