

# Gastrointestinal Oncology Division

## Introduction

The clinical subjects treated in the Gastro-intestinal Oncology Division are cases of early and advanced esophageal cancers as well as cases of gastric and colorectal cancers with distant metastasis. Although chemotherapy for gastrointestinal cancers has been developed, its efficacy in general is insufficient. Therefore, we are trying to investigate and establish new modalities of chemotherapy treatment for these patients.

## Routine Activities

The staff of the division consists of five medical oncologists and five residents. All members of our division discuss the treatment for each patient weekly. Inter-group meetings with each surgical division (the Esophageal, Gastric, and Colorectal Surgery Divisions) and the Radiation Oncology Division are held weekly to decide treatment strategies for each individual case or to discuss the future strategy for the disease. Palliative care to improve the physical and psychological aspects of the patients' quality of life is another important theme discussed in staff meetings. Anesthesiologists and psycho-oncologists join in and advise us on how to care for the patients during their palliative stage.

In 2004, we treated 1883 hospitalized patients (780 of whom were newly diagnosed). Of these patients, 385 were entered in protocol studies.

## Research Activities

A phase II study of single-agent docetaxel was conducted to evaluate the activity and toxicity in patients with metastatic esophageal cancer. Of 52 patients enrolled in this study, 36 had received prior platinum-based chemotherapy. Ten of 49 evaluable patients (20%) showed a partial response. Grade 3 or 4 neutropenia was noted in 43 of 49 patients, and nine of 49 patients developed febrile neutropenia. We concluded that docetaxel as a single agent was effective in esophageal cancer, but careful management of neutropenia was needed (K Muro).

A phase II study of sequential methotrexate and 5-fluorouracil chemotherapy against peritoneally disseminated gastric cancer with malignant ascites

was conducted. The response rate of ascites was 35.1%. We concluded that sequential methotrexate and 5-fluorouracil therapy was effective with malignant ascites with acceptable toxicity and warrant further investigation in a phase III setting (T Yamao).

A phase II study of an oral regimen consisting of uracil/tegafur(UFT) and leucovorin(LV) was conducted to compare the efficacy, toxicities, and pharmacokinetics between Japanese and American patients with metastatic colorectal cancer. The efficacy and pharmacokinetic parameters of UFT/LV was comparable in Japanese and American patients, however, a difference in toxicity profile, in particular diarrhea, was noted (K Shirao). A phase I/II study of irinotecan, 5-fluorouracil and l-leucovorin combination chemotherapy, which is widely used in Western patients with metastatic colorectal cancer, was conducted in Japanese patients. Our results confirmed that this combination therapy is safe and efficacious for Japanese patients, too (Goto). A phase II study of S-1 for colorectal cancer was conducted to evaluate the objective response rate and toxicities. The response rate was 39.5%. Major adverse reactions included myelosuppression and gastrointestinal toxicities; most cases were grades 1 or 2 (K Shira).

A phase I and pharmacokinetic study of MCC-465 was conducted in patients with metastatic stomach cancer (Y Matsumura). MCC-465 is an immunoliposome-encapsulated doxorubicin. The liposome is tagged with polyethylene glycol and the F(ab')<sub>2</sub> of a monoclonal antibody named GAH, a human antibody obtained by the hybridoma technique. Immunohistochemistry with GAH revealed that 94% of surgical specimens of colorectal cancer were GAH-positive (T Hamaguchi). These results warrant a further clinical trial of MCC-465 for patients with metastatic colorectal cancer.

## Clinical Trials

We carried out clinical trials in collaboration with the Surgery and Radiation Oncology Divisions at the National Cancer Center Hospital and other institutes. Summary of clinical trials are shown in the table.

### 1. Esophageal Cancer

A phase III study of preoperative versus post-

operative chemotherapy (5FU+CDDP) is ongoing (JCOG9907). On the basis of results from a phase I/II study of low dose FP/RT (low dose of 5-FU + low dose CDDP + radiation) (JCOG9907), a comparative phase II/III study of low dose FP/RT versus standard dose FP + radiation against T4 cancers was started in 2004 (JCOG 0303). Also, a phase I study of 5FU+CDDP+RT (50.4Gy) against stage II/III, and a phase I study of 5FU+CDDP+Taxotere against stage IV is ongoing.

### 2. Gastric cancer

A phase III study of three arms (5-FU/CPT-11+CDDP/S1) is ongoing (JCOG9912). On the basis of results from a phase II study of methotrexate plus 5-FU (JCOG 9603) in patients with malignant ascites, the phase III study of this combination versus 5-FU alone against peritoneal dissemination is ongoing (JCOG0106).

### 3. Colorectal Cancer

A phase III study of adjuvant chemotherapy (5FU/LV versus UFT/LV) after surgery is ongoing

(JCOG0205). Also, a phase I study of CPT-11+5FU+leucovorin (FOLFIRI) via the central vein using an ambulatory pump, a phase I/II study of the combination of intrahepatic arterial infusion of 5-FU plus intravenous CPT-11 (JCOG0208), and a phase II study of CPT-11+S-1 is ongoing.

### 4. Others

A phase I study of weekly MCC-465 (Adriamycin-encapsulated liposomes conjugated with monoclonal antibody against a cell surface molecule of gastrointestinal cancers) is ongoing. Also, a phase I study of new agent monoclonal antibody IMC-C225 (Cetuximab), which is an anti-epidermal growth factor receptor (EGFr), for the patients with EGFr-positive tumors is ongoing. A study of chemosensitivity by cDNA microarray analysis of gene-expression profiles was started in 2003 and is presently ongoing. Also, a pharmacogenomic study regarding some enzymes involved in 5-FU and CPT-11 metabolism was completed in 2004.

● K. Shirao ●

Number of Patients Treated			
	No. of hospitalized pts	No. of newly diagnosed pts	No. of pts enrolled protocol
1) Esophageal cancers	841	234	
surgery→5FU+CDDP vs surgery (phase III)			7
standard 5FU+CDDP+RT vs low dose 5FU+CDDP+RT (phase II/III)			3
5FU+CDDP+RT(50.4Gy) (phase I)			9
5FU+CDDP+Taxotere (phase I)			2
MCC465 (phase I)			1
chemo-sensitivity by cDNA microarray analysis			23
2) Gastric cancers	682	210	
5-FU vs CDDP+CPT-11 vs S1 (phase III)			34
5FU+MTX vs 5FU (Phase III)			13
MCC465 (phase I)			4
pharmacogenomics (5FU)			41
pharmacogenomics (CPT-11)			1
chemo-sensitivity by cDNA microarray analysis			27
3) Colorectal cancers	310	295	
surgery→5FU/LV vs surgery→UFT/LV (phase III)			54
TS-1/CPT-11 (phase II)			36
5FU/LV+CPT-11 (FOLFIRI) (Phase I)			15
5FU(intrahepatic arterial infusion)+CPT-11(systemic) (phase I/II)			1
Cetuximab (phase I)			17
Bevacizumab+5FU/LV (phase I/II)			4
NK105 (phase I)			1
pharmacogenomics (5FU)			23
pharmacogenomics (CPT-11)			15
chemo-sensitivity by cDNA microarray analysis			49
4) Others	50	41	
NK105 (phase I)			5
Total	1883	780	385