

Gastrointestinal Oncology Division

Introduction

The clinical subjects treated in the Gastrointestinal 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 establish new modalities of chemotherapy for these patients.

Routine Activities

The staff of the division consists of five medical oncologists and four 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 2003, we treated 1466 hospitalized patients (670 of whom were newly diagnosed). Of these patients, 276 were entered in protocol studies.

Research Activities

A phase II study of biweekly irinotecan and mitomycin C (MMC) combination therapy was designed to evaluate the efficacy and safety for patients with fluoropyrimidine-resistant advanced colorectal cancer. Among the 41 patients enrolled, objective responses were observed in 14 patients (34%). The median time to progression was 4.2 months, and the median survival time was 11.9 months. Grade 3 or 4 neutropenia, the most common toxic effect, occurred in 20 patients (49%). Grade 3 or 4 thrombocytopenia occurred in four patients (10%) and grade 3 diarrhea in one patient. Our results suggest that irinotecan and MMC combination therapy is effective and well tolerated in patients with

fluoropyrimidine-resistant metastatic colorectal cancer (Y Yamada).

A randomized study was designed to compare the effects of dexamethasone (Dex) with those of a placebo for delayed emesis, anorexia and fatigue induced by irinotecan. Sixty-eight patients (35 receiving Dex, 33 receiving the placebo) enrolled in this study. Although delayed emesis was completely prevented in most of patients in both groups, anorexia and fatigue were more completely prevented in those in the Dex group (Dex, 62.9% and 77.1%, placebo, 39.4% and 57.6%, respectively). The effect of Dex on improving simultaneous prophylaxis against all three symptoms was almost significant. These results suggest that treatment with Dex may be beneficial to reduce post-chemotherapy symptoms induced by irinotecan, specifically anorexia and fatigue (A Inoue).

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.

1. Esophageal Cancer

A phase III study of preoperative versus postoperative chemotherapy (5-FU+CDDP) is ongoing (JCOG9907). On the basis of results from a phase II study of chemotherapy (5-FU+CDDP) and radiotherapy against stage I cancers (JCOG9708), a comparative phase III study of surgery versus chemoradiation (5-FU+CDDP+radiation) against stage I cancers is planned as JCOG study. Also, 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 will be started in 2004 as JCOG study. Also, a phase I/II study of Taxotere+5-FU+CDDP against stage IV metastatic disease is in the planning stage.

2. Gastric cancer

A phase II study of CPT-11+MMC as second-line chemotherapy against metastatic disease (JCOG0109DI), and phase II study of weekly Taxol against pretreated patients were completed in 2003. A phase II study of neo-adjuvant chemotherapy

(CPT-11+CDDP) was finished in 2003 and a new phase II study of neo-adjuvant chemotherapy (S-1+CDDP) was started in 2003 (JCOG0210). 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 has been started in 2002 (JCOG0106) and is presently ongoing. Also, a study of chemo-sensitivity by cDNA microarray analysis of gene-expression profiles was started in 2003.

3. Colorectal Cancer

A phase I/II study of Oxaliplatin+5-FU+leucovorin as first-line chemotherapy was completed in 2003. A phase II study of new agent capecitabine, which is a fluoropyrimidine carbamate with antineoplastic activity, has been started in 2003 and the enrollment was finished in 2003. A phase I/II study of CPT-11+5-FU+leucovorin (de Gramont regimen) via the central vein using an ambulatory pump, and a phase I/II study of the combination of intrahepatic arterial infusion of

5-FU and intravenous CPT-11 (JCOG0208) were started in 2003. Also, a phase III study of adjuvant chemotherapy (5-FU/LV versus UFT/LV) after surgery has been started in 2003 (JCOG0205) and is presently ongoing.

4. Others

A phase I study of the new agent NK-911 (Adriamycin-encapsulated polymeric micelle) was completed. Also, a phase I study of Etoposide B (new class of microtubule-stabilizing agent) has been started in 2002 and is completed in 2003. 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 pharmacogenomic study regarding some enzymes involved in 5-FU and CPT-11 metabolism is ongoing. Furthermore, 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 will be started 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	638	197	
surgery->CDDP/5FU vs CDDP+5FU->surgery (phase III)			9
MCC465 (phase I)			2
Etoposide B (phase I)			1
2) Gastric cancers	580	225	
5-FU/ CDDP+CPT-11/S1 (phase III)			36
MCC465 (phase I)			1
CPT-11+MMC (phase II)			8
5FU+MTX/5FU (Phase III)			17
weekly taxol (Phase II)			30
chemo-sensitivity by cDNA microarray analysis			9
pharmacogenomics (5FU)			47
pharmacogenomics (CPT-11)			2
3) Colorectal cancers	205	217	
Oxaliplatin+5FU/LV (Phase I/II)			5
MCC465 (Phase I)			3
Etoposide B (phase I)			4
CPT-11+5FU/I-LV (phase I)			10
surgery->5FU/LV vs surgery->UFT/LV (phase III)			35
Capecitabine (phase II)			10
pharmacogenomics (5FU)			30
pharmacogenomics (CPT-11)			16
4) Others	43	31	
pharmacogenomics (5FU)			1
Total	1466	670	276