

Hepatobiliary and Pancreatic Oncology

Introduction

The division of Hepatobiliary and Pancreatic Oncology deals with cancers of the liver, biliary system, and pancreas. The prognosis of patients with advanced or metastatic disease of hepatobiliary or pancreatic cancer is dismal. Various combination therapies are often required to treat cancers at these sites, and treatment strategies are carefully discussed by surgeons, radiologists, and medical oncologists at our conferences. We have been trying to develop more effective treatments for these cancers.

Routine Activities

Systemic chemotherapy regimens for hepatobiliary and pancreatic cancers remain unsatisfactory and inadequate. We have been evaluating systemic chemotherapy protocols in clinical trials and using some regimens as standard treatments in patients with distant metastases or locally advanced disease. We have been using gemcitabine to treat pancreatic cancer patients with unresectable lesions since its approval by the Ministry of Health, Labour and Welfare in 2001. However, the therapeutic effect of gemcitabine remains unsatisfactory, and we have been performing clinical trials of new regimens. Many hepatocellular carcinoma (HCC) and biliary tract cancer patients require systemic chemotherapy. However, no standard regimen of systemic chemotherapy has been established, and we have also been conducting clinical trials in such patients.

Percutaneous ablation therapy, including ethanol injection (PEI) or radiofrequency ablation (RFA), is indicated as a standard treatment for HCC in patients having no more than 3 tumors, each less than 3 cm in diameter. RFA has been the treatment of first choice for small HCCs since 2000, because a wide necrotic area can be obtained during a single treatment session and a shorter hospital stay is required than PEI. Transcatheter arterial chemoembolization (TACE) is routinely used to treat advanced or recurrent HCC when a hepatectomy or percutaneous ablation therapy is not indicated. Hepatic arterial infusion (HAI) chemotherapy with cisplatin or epirubicin has been used to treat very advanced HCC, for which TACE is not indicated.

Radiotherapy is also used to treat hepatobiliary and pancreatic cancer. We completed a phase II study of proton beam radiotherapy for HCC in June 2001 and now utilize this highly advanced medical technology clinically. Patients with unresectable advanced bile duct cancer have been treated with radiation therapy consisting of external beam radiation therapy (EBRT) and intraluminal brachytherapy with Ir192 in a phase II study since 1999.

Percutaneous transhepatic biliary drainage (PTBD), cholangiography, and cholangioscopy are performed in patients with obstructive jaundice to relieve jaundice and determine the cause of the bile duct obstruction. Metallic stents are inserted in patients with obstructive jaundice to improve their quality of life, and the fact that PTBD tubes can be removed if a stent is inserted, further improves patients' quality of life.

Abdominal ultrasonography plays a very important role both in screening for malignancies and performing thorough examinations, especially in hepatobiliary and pancreatic cancers. A total of 5,029 patients were examined by ultrasonography in 2005. We also evaluate tumor vascularity with color Doppler ultrasound and/or contrast-enhanced ultrasound to diagnose of hepatic tumors, when it is difficult to make the differential diagnosis by conventional ultrasound examinations.

Research Activities and New Developments

Systemic chemotherapy for hepatobiliary and pancreatic cancers remains unsatisfactory and adequate. We have been conducting and performing clinical trials to identify more promising treatments for patients with distant metastases or locally advanced disease. We have also retrospectively studied patients with these cancers treated by non-surgical modalities to assess survival and identify prognostic factors in such patients. The following clinical trials were completed or in progress in 2005:

1. Hepatocellular carcinoma
 - 1) A phase I study of systemic chemotherapy with BAY 43-9006 (single-center trial). BAY 43-9006 is a potent inhibitor of Raf kinase and VEGFR2 signaling. The study was completed

as in 2005.

- 2) A phase I/II study of systemic chemotherapy with UFT+mitoxantron (single-center trial). The phase I part of the study was completed in August 2005 and the recommend dose was determined. The phase II study is currently in progress.
- 3) A phase II study of HAI with CDDP for HCC with portal vein tumor thrombus (multi-center trial), which was begun in July 2004.
- 4) A phase I/II study of HAI with 5-FU, CDDP, and mitxantrone (FMP regimen) for advanced HCC (multi-center trial), which was begun in October 2005.
- 5) A phase III study of NIK333 as adjuvant therapy after curative treatment including surgery and ablation therapy for HCC (multi-center trial), which was begun in May, 2005. NIK333 is an analogue of vitamin A, and is expected to prevent development of new HCC lesions. The study is a placebo-controlled

randomized trial.

2. Biliary tract cancer
 - 1) A phase II study of UFT plus doxorubicin for unresectable biliary tract cancer (multi-center study), which was begun in April 2005.
3. Pancreatic cancer.
 - 1) A phase II study of gemcitabine+S-1 for metastatic disease (multi-center trial), completed in July 2005.
 - 2) A phase I study of S-1 and concurrent radiotherapy for locally advanced disease (multi-center trial), completed in November 2005
 - 3) A phase II study of gemcitabine+S-1 chemotherapy followed by chemoradiotherapy with a radiotherapy dose of 30 Gy for locally advanced disease (single-center trial), which was begun in March 2005.

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Number of operation cases

	2003	2004	2005
HCC	91	116	77
Biliary tract	43	49	42
ICC		16	17
ECC		13	10
GB		19	13
Amp		1	2
Pancreas	91	103	104
Locally advanced	67	76	76
Metastatic	24	27	28
Others	21	17	29
Total	246	285	252

ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; GB, gallbladder cancer; Amp, ampulla of Vater cancer

Treatment methods and number of the patients as the first line in 2005

	HCC	Biliarytract	Pancreas
Percutaneous ablation therapy	22	0	0
RFA or RFA+PEI	21	0	0
PEI	1	0	0
Transcatheter treatment	40	1	0
TACE	28	0	0
HAI	12	1	0
Radiation therapy	4	0	14
Photon	1	0	0
Proton	3	0	0
Photon+RALS	0	0	0
RT+chemotherapy	0	0	14
Other	0	0	0
Systemic chemotherapy	4	39	82
Best supportive care	7	2	8
Total	77	42	104

HCC: hepatocellular carcinoma, PEI: percutaneous ethanol injection, RFA: radio-frequency ablation therapy, TACE: transcatheter arterial chemoembolization, HAI: hepatic arterial infusion of anti-cancer drug, RALS: remote after loading system using Ir192