

Hepatobiliary and Pancreatic Oncology Division

Introduction

The Hepatobiliary and Pancreatic Oncology Division treats tumors originating in the liver, biliary system or pancreas, for example, hepatocellular carcinoma (HCC), biliary tract cancer, and pancreatic cancer. As part of the multi-disciplinary care given at the National Cancer Center Hospital, we work closely with surgeons and radiologists who have special expertise in these areas. We also conduct research into the patho-physiology of hepatobiliary and pancreatic tumors and to develop new and more effective diagnostic methods and treatments.

Routine Activities

The division consists of three staff oncologists and three to four residents. In 1990, the division began using percutaneous ethanol injection (PEI) to treat patients with small HCCs. In 1999, radiofrequency ablation therapy (RFA) was introduced clinically as an alternative to PEI. Based on long-term observations of PEI-treated patients, we have employed percutaneous ablation therapy as a valuable alternative to surgery for most patients with HCC nodules equal to or less than 3, all of which are smaller than 3 cm in diameter. We also perform transcatheter arterial embolization (TAE), mainly in patients with multiple HCC nodules. Patients with locally advanced pancreatic cancer receive chemoradiotherapy, which has shown some survival benefit and has improved symptoms such as upper abdominal pain to a significant degree. In patients with metastatic and recurrent pancreatic cancer, chemotherapy is performed in clinical practice or as a clinical trial to develop active treatment.

Most patients with hepatobiliary and pancreatic tumors, whether they undergo surgical or nonsurgical treatment, are hospitalized in the Hepatobiliary and Pancreatic Ward. Case conferences are held weekly with surgeons to determine treatment strategies for these patients. Rounds and conferences for patients admitted to the division are made by all staff oncologists and residents every morning and evening.

Research Activities

Efficacy and toxicity of radiotherapy combined

with gemcitabine were evaluated in a phase II study for locally advanced pancreatic cancer, because gemcitabine has been reported to be a potent radiosensitizer in human pancreatic cell lines (Okusaka T, et al.). Forty-two patients with pancreatic cancer which was unresectable but confined to the pancreatic region were treated with external-beam radiation (50.4 Gy in 28 fractions over 5.5 weeks) and weekly gemcitabine (250 mg/m², 30-min infusion). The major toxicity was leukopenia and anorexia. There was one death attributed to duodenal bleeding and sepsis. The median survival time was 9.5 months, and the 1-year survival rate was 28%. The median progression-free survival time was 4.4 months. In 35 patients with documented disease progression at the time of analysis, 34 (97%) showed distant metastasis as the cause of the initial disease progression. The chemoradiotherapy used in this study has a moderate activity against locally advanced pancreatic cancer and an acceptable toxicity profile. Future investigations for treatment with more systemic effects are warranted.

A phase II study was conducted to investigate the efficacy and safety of an oral fluoropyrimidine derivative, S-1, in patients with advanced biliary tract cancer (Ueno H. et al.). Patients with pathologically confirmed advanced biliary tract cancer, a measurable lesion, and no history of radiotherapy or chemotherapy were enrolled. S-1 was administered orally (40 mg/m² b.i.d.) for 28 days, followed by a 14-day rest period. A pharmacokinetic study was performed on day 1 in the initial eight patients. In all, 19 consecutive eligible patients were enrolled. The site of the primary tumor was the gallbladder (n=16), the extrahepatic bile ducts (n=2), and the ampulla of Vater (n=1). Four patients achieved a partial response, giving an overall response rate of 21.1%. The median time-to-progression and median overall survival period were 3.7 and 8.3 months, respectively. Although grade 3 anorexia and fatigue occurred in two patients each (10.5%), no grade 4 toxicities were observed. The pharmacokinetic parameters after a single oral administration of S-1 were similar to those of patients with other cancers. S-1 exhibits definite antitumor activity and is well tolerated in patients with advanced biliary tract cancer.

We investigated the maximum-tolerated dose of hyperfractionated radiation therapy with protracted 5-fluorouracil (5-FU) infusion in patients with locally advanced, unresectable pancreatic cancer (Ueno H. et al.). Five cohorts of patients were scheduled to receive escalating doses of hyperfractionated radiation therapy (range, 45.6-64.8 Gy). All patients received two fractions of 1.2 Gy each (separated by 6h) per day for 5 days a week, and received protracted 5-FU infusion (200 mg/m²/day) during the radiation course. The maximum-tolerated dose was defined as one dose level below the dose at which more than one third of 3-6 patients experienced dose-limiting toxicity. Twenty-nine patients were enrolled in this study. The most common toxicities were nausea/vomiting and anorexia. Although 1 patient developed bleeding from a gastric ulcer 3 months after the completion of chemoradiotherapy, the maximum-tolerated dose was not reached even at the highest

dose level (level 5, 64.8 Gy). The median survival time was 12.2 months and the 1-year survival rate was 55.0%. The toxicity associated with our regimen was tolerable up to dose level 5 (64.8 Gy). We are currently conducting a phase II study of this hyperfractionated radiation therapy with protracted 5-FU infusion at a dose of 64.8 Gy.

Clinical Trials

Sixteen clinical trials are ongoing, including two phase III trials: TAE versus intra-arterial chemotherapy in HCC patients and adjuvant chemotherapy versus no therapy in PC patients. Four phase II clinical trials were started in 2004: gemcitabine/S-1 in pancreatic cancer patients, S-1 in patients with gemcitabine-refractory pancreatic cancer, gemcitabine in patients with pancreatic endocrine cancer, and adriamycin and UFT in biliary tract cancer patients. ● T. Okusaka ●

Total number of inpatients								
Year			1999	2000	2001	2002	2003	2004
Liver	HCC		227	309	276	381	447	502
	Intrahepatic cholangiocarcinoma		38	38	55	31	2	7
	Extrahepatic bile duct		13	14	1	25	17	17
	Gall bladder		36	46	36	36	21	35
	Pancreas		132	202	247	254	380	243
Total			446	609	615	727	867	804

Number of new inpatients									
Year			1999	2000	2001	2002	2003	2004	
Liver	HCC	Ethanol injection	27	18	20	26	33	11	
		Radiofrequency ablation	9	13	7	9	16	29	
		Transcatheter arterial embolization	16	52	56	45	64	61	
		Intra-arterial chemotherapy	25	27	42	19	27	11	
		Systemic chemotherapy	9	17	7	9	8	10	
		Intrahepatic cholangiocarcinoma	11	6	14	11	4	7	
		Extrahepatic bile duct	5	2	2	8	4	11	
		Gallbladder	12	12	17	18	12	15	
		Papilla of Vater	2	2	1	1	2	1	
		Pancreas Locally advanced type	22	35	35	48	51	45	
		Metastatic type	30	47	60	58	112	95	
Total			168	231	261	252	333	296	