

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 (BTC), and pancreatic cancer (PC). 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 PC 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 PC, 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

A phase II study of SM-11355 was conducted to evaluate the anti-tumor activities and the toxicity in chemotherapy-naïve patients with HCC (Okusaka T, et al.). SM-11355, a lipophilic platinum derivative, is a novel intra-arterial chemotherapeutic agent for HCC. Sixteen patients were treated with transcatheter arterial injection of SM-11355-lipiodol emulsion. Complete response (CR) was defined as disappearance or 100% necrosis of all tumors, and lipiodol accumulation in tumors was regarded as indicating necrosis. Nine patients (56%) achieved CR. The grade 3 toxicities were neutropenia (19%), total bilirubin elevation (19%), AST elevation (44%), and ALT elevation (19%). None of the patients showed grade 4 toxicities or episodes of renal dysfunction. Other common adverse effects were eosinophilia (100%) and pyrexia (94%). Intra-arterial chemotherapy with SM-11355, which was well tolerated, showed promising anti-tumor activity in patients with HCC.

Chemo-naïve patients with advanced BTC were treated with cisplatin, epirubicin, and continuous-infusion of 5-FU (CEF therapy) to clarify the efficacy and toxicity (Morizane C. et.al.). Thirty-seven patients were enrolled into this study. A partial response was obtained in 7 patients (19%). The median survival time was 176 days. Grade 3 to 4 adverse effects were leukocytopenia (59%), neutropenia (76%), nausea/vomiting (30%), and alopecia (35%). These toxicities were generally reversible, but two patients died of neutropenic sepsis. CEF therapy has marginal antitumor activity against advanced BTC, although hematological toxicity was

the most major and frequent toxicity.

A phase II study was conducted to evaluate the activity, toxicity, and pharmacokinetics of S-1 in advanced BTC patients (Ueno H. et.al.). Out of total 19 evaluable patients, objective responses were observed in 4 patients (21.1%); 9 patients were no change and 5 patients were progressive disease. Median survival was 252 days. The grade 3 anorexia and fatigue occurred in 2 patients respectively (10.5%). Also grade 3 erythrocytopenia, neutropenia, γ -GTP increase, hyponatremia, fever, stomatitis, nausea, and diarrhea occurred in 1 patient respectively (5.3%). Pharmacokinetic parameters after single oral administration of S-1 in patients with BTC were almost the same as those with gastric, colorectal, breast, and pancreatic cancer. S-1 is active and well

tolerated in BTC patients, which will be confirmed in following larger phase II trial.

Clinical Trials

Twenty 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. Five clinical trials were started in 2003 including two phase II trials (S-1 in PC patients and NK911 in PC patients), and a phase I/II trial (TAC101 in HCC patients), and two phase II trials (gemcitabine/S-1 in PC patients and adjuvant chemotherapy after chemoradiotherapy in PC patients).

● T. Okusaka ●

Protocols	
Phase I	3
Phase I-II	2
Phase II	12
Phase III	2
Pharmacogenomics	1

PEI and RFA for Small HCC* (1990-2003)				
		Survival		
		1-yr	3-yr	5-yr
Primary pts	238	99%	80%	53%
Post-op. pts	119	97%	77%	47%

*Three or less nodules, all smaller than 3 cm

Chemoradiotherapy for Pancreatic Cancer (1993-2003)			
No. pts	Median survival	1-yr survival	Response rate
274	9.7 months	39%	15.0%

Systemic Chemotherapy (1990-2003)*			
	No. pts	Response rate	Median survival
HCC	124	20%	8.2 mo
Biliary tract ca.	117	19%	8.2 mo
Pancreatic ca.	330	10%	6.4 mo

*Data show the numbers of chemo-naive patients