30. Richards DA, Sherwood RA, Ndebele D, et al: Determination of plasma cytidine deaminase activity by HPLC. Biomed Chromatogr 2:148-151, 1987

31. Benjamini Y, Hochberg Y: Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Statist Soc Ser B 57:289-300, 1995

32. Bhargava P, Marshall JL, Fried K, et al: Phase I and pharmacokinetic study of two sequences of gemcitabine and docetaxel administered weekly to patients with advanced cancer. Cancer Chemother Pharmacol 48:95-103, 2001

33. Johansson E, Mejlhede N, Neuhard J, et al: Crystal structure of the tetrameric cytidine deaminase from Bacillus subtilis at 2.0: A resolution. Biochemistry 41:2563-2570, 2002

34. Costanzi S, Vincenzetti S, Vita A, et al: Human cytidine deaminase: Understanding the catalytic mechanism. Nucleosides Nucleotides Nucleic Acids 22:1539-1543, 2003

35. Kreis W, Lesser M, Budman DR, et al: Phenotypic analysis of 1-B-D-arabinofuranosylcytosine deamination in patients treated with high doses and correlation with response. Cancer Chemother Pharmacol 30:126-130, 1992

36. Abbruzzese JL, Grunewald R, Weeks EA, et al: A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. J Clin Oncol 9:491-498, 1991

37. Nishida M: Pharmacological and clinical properties of Xeloda (capecitabine), a new oral active derivative of fluoropyrimidine [Japanese]. Nippon Yakurigaku Zasshi 122:549-553, 2003

38. Fukunaga AK, Marsh S, Murry DJ, et al: Identification and analysis of single nucleotide polymorphisms in the gemcitabine pharmacologic pathway. Pharmacogenomics J 4:307-314, 2004

39. Jahns-Streubel G, Reuter C, Auf der Landwehr U, et al: Activity of thymidine kinase and of polymerase alpha as well as activity and gene expression of deoxycytidine deaminase in leukemic blasts are correlated with clinical response in the setting of granulocyte-macrophage colony-stimulating factor-based priming before and during TAD-9 induction therapy in acute myeloid leukemia. Blood 90: 1968-1976, 1997

40. Sherwood RA: The measurement of nucleoside deaminases by high performance liquid chromatography and their use in clinical chemistry. Biomed Chromatogr 5:235-239, 1991

Acknowledgment

We thank Emiko Jimbo, Miho Akimoto, Atsuko Watanabe, Tomoko Chujo, Makiyo Iwamoto, and Mamiko Shimada for assistance in sample collection and management, and Chie Sudo for secretarial assistance.

Jpn J Clin Oncol 2007;37(11)843–851
doi:10.1093/jjco/hym116

A Multi-center Retrospective Analysis of Survival Benefits of Chemotherapy for Unresectable Biliary Tract Cancer

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Received April 27, 2007; accepted July 28, 2007; published online October 17, 2007

Background: This study examined the effect of five systemic chemotherapy regimens on survival in patients with unresectable biliary tract cancer (BTC) as compared with the best supportive care (BSC).
Methods: This study retrospectively reviewed data from 413 consecutive patients with BTC who were seen at any of nine central hospitals in Japan between April 2000 and March 2003. Patients were eligible if they had intra- or extrahepatic cholangiocarcinoma or gallbladder cancer with no prior chemotherapy. Hazard ratios of treatment regimens were estimated using the Cox proportional hazard model and the propensity score method.
Results: Three-hundred and four patients were enrolled: 125 (41.1%) received BSC and 179 (58.9%) took chemotherapy. Of those who received chemotherapy, 58 (19.1%) took gemcitabine (GEM), 45 (14.5%) took a cisplatin (CDDP)-based regimen, 30 (9.9%) took a 5-fluorouracil (5-FU)-based regimen, 27 (8.9%) took 5-FU + doxorubicin + mitomycin (FAM) and 20 (6.6%) took S-1. The response rate was 8.4% ($n = 15$). The CDDP-based regimen was associated with a high frequency of toxicity symptoms. The adjusted hazard ratio for GEM in the Cox regression was 0.53 (95% CI 0.34–0.82) and the hazard ratio for the CDDP-based regimen was 0.49 (95% CI 0.36–0.99).
Conclusion: Chemotherapy with GEM may benefit patients with BTC.

Key words: biliary tract cancer – chemotherapy – survival – retrospective study – clinical trial

INTRODUCTION

Biliary tract cancer (BTC) is a relatively rare disease in the United States and Western Europe (1), but a frequent and serious cancer in Japan. It is the sixth leading cause of cancer death in Japan, killing approximately 15 000 people every year (2), and the incidence is increasing. BTC have traditionally been divided into cancers of the gallbladder, the extrahepatic bile ducts and the ampulla of Vater, whereas intrahepatic bile-duct cancers have been classified as liver cancer (1). Lately, however, the term BTC has been used to include the gallbladder, the intrahepatic cholangiocarcinoma, the extrahepatic cholangiocarcinoma and the ampulla of Vater (1). Worldwide, incidence and mortality rates of intrahepatic cholangiocarcinoma are increasing, while incidence rates of extrahepatic cholangiocarcinoma and gallbladder cancer are slightly decreasing (3).

Surgical resection is the only curative treatment for BTC, but it is only feasible if the cancer is detected early. The 5-year survival rate for resectable patients is around 40% (1). Because of the lack of early symptoms, most patients are diagnosed at an advanced stage, by which time the cancer has often metastasized or invaded the adjacent liver or

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hepatic artery. Such patients are not candidates for surgical resection and their prognosis is extremely poor (1). It remains unclear if chemotherapy could benefit patients with unresectable BTC(1–2). No chemotherapy or radiotherapy has yet been proven to substantially improve outcomes (1).

Many clinical trials of single- and multi-drug regimens have been conducted for BTC, but the reported response rates, toxicity and survival times have been variable. Most of the clinical trials conducted to date have been phase II trials. Only three phase III trials (4–6) and two observational studies (7,8) have been published, and limited information from real-world clinical practice is available. In the phase III study by Glimelius et al. (5), although overall survival was superior in the treated group, 6 m vs 2.5 months in the best supportive care (BSC) group, the difference did not remain significant. This result was from subgroup analysis in the study and might be below the statistical power.

Although the efficacy of conventional systemic chemotherapy seems negligible, there is no agreement on the standard chemotherapeutic regimen to replace it. A large number of multi-drug regimens have been tested in phase II trials and the results suggest that patients with advanced BTC might benefit from (1) 5-fluorouracil (5-FU) and cisplatin (9,10); (2) epirubicin (11); (3) S-1 (12); (4) 5-FU, leucovorin, and mitomycin C (13); (5) uracil-tegafur (14); (6) uracil-tegafur and doxorubicin (15); (7) gemcitabine (GEM) (16–21); (8) GEM and 5-FU (22,23); (9) GEM, 5-FU, and leucovorin (24,25); (10) GEM and cisplatin (26–30); (11) GEM and capecitabine (31–33); (12) GEM and oxaliplatin (34–36); and (13) oxaliplatin (37).

These data require further investigation. Many of the chemotherapeutic regimens listed above have been investigated in small, uncontrolled studies, with generally disappointing results. The major weaknesses of these studies in establishing a standard therapy are the rarity and heterogeneity of BTC, small sample sizes and the lack of a control group to provide data on survival times. Which regimen is appropriate as a reference arm in a large phase III trial remains unknown.

The objective of this study was to clarify the impact of systemic chemotherapy on BTC, particularly unresectable biliary and gallbladder cancer, using a multicenter observational study in Japan. We analyzed survival time in a group of patients who were treated with systemic chemotherapy or BSC.

PATIENTS AND METHOD

Study Design

We retrospectively reviewed 413 unresectable BTC patients seen between April 2000 and March 2003 at nine central hospitals in Japan. Patients were eligible if they had unresectable, locally advanced or metastatic adenocarcinoma arising from intrahepatic cholangiocarcinoma ($n = 126$), extrahepatic cholangiocarcinoma ($n = 97$), gallbladder cancer ($n = 169$) or papilla of Vater cancer ($n = 21$). Two-hundred and seven patients were treated with systemic chemotherapy, seven with arterial injection chemotherapy, 45 with radiotherapy, 15 with chemoradiotherapy and 137 received BSC.

We excluded patients with cancer of the papilla (because the number of patients was very small), arterial-injection chemotherapy, unclassified chemotherapy, radiotherapy, prior chemotherapy and missing clinical variables (serum carbohydrate antigen 19-9 (CA19-9) or carcinoembryonic antigen (CEA)) from the analysis (Fig. 1).

Classification Of Chemotherapy Regimens

Chemotherapy regimens were classified into five types: 5 FU-based; S-1 alone; gemcitabine (GEM) alone; 5-FU, doxorubicin and mitomycin C (FAM); and cisplatin (CDDP)-based regimens. The 5 FU-based regimens comprised uracil-tegafur alone, 5-FU alone and 5-FU plus leucovorin. The CDDP-based regimen was of four types: a combination of CDDP, epirubicin and 5-FU; 5-FU plus CDDP; CDDP plus etoposide; or CDDP alone. Patients treated with irinotecan alone, low-dose 5-FU plus CDDP, carboplatin alone or doxorubicin plus vincristine were unclassified and excluded from the analysis.

The pathology report used cytological examination for the possible cases or clinical diagnosis for impossible other cases. Toxicity was scored weekly according to WHO criteria (38). Follow-up computed tomography was performed after every course of chemotherapy to objectively assess tumor response according to the Response Evaluation Criteria in Solid Tumors (39) at each hospital.

Definition of Clinical Variables

Clinical variables used in this study were treatment, tumor type, age, gender, performance status (PS), status of surgery, evidence for unresectability, biopsy, hepatic metastasis, pleural metastasis, distant lymph node metastasis, lung metastasis, bone metastasis, ascites, biliary drainage, total bilirubin, CEA level and CA19-9 level.

These variables were measured immediately before chemotherapy (for the treated group) or at the time of diagnosis (for the BSC group). Continuous variables were dichotomized using the following cutoffs: age, 60 years; CEA, 10 ng/ml; CA19-9, 1000 U/ml; and total bilirubin, 3 mg/dl. Categorical variables such as pre-surgery, biopsy and ascites were dichotomized to presence or absence of the characteristic. PS categories were collapsed into 3 levels: 0, 1 and 2–4.

Statistical Methods

Overall survival was measured from the first day of treatment (chemotherapy group) or from the day of diagnosis (BSC group) to the date of death or last visit. The study enrolled period ended on March 31, 2003, and observations on those patients remaining at the end of the study were censored. Survival curves were calculated by the Kaplan–Meier

Figure 1. Flow chart of patient selection. CEA, carcinoembryonic antigen; CA, serum carbohydrate antigen.

method (40). Differences in survival among subgroups according to each factor were evaluated by logrank tests. Hazard ratios and 95% confidence intervals (CI) were estimated by the Cox regression (41). Multivariate Cox regression (41) and the Cox regression by modeling the propensity score were performed for adjustment of confounders (42,43). We used 16 covariates (tumor type, age, gender, PS, status of surgery, evidence for unresectability, biopsy, hepatic metastasis, peritoneal metastasis, distant lymph node metastasis, lung metastasis, ascites, biliary drainage, total bilirubin, CEA level and CA19-9 level) for adjustment. Statistical significance was defined as a two-sided *P*-value of 0.05 or less. The analyses were performed using the statistical software JMP 5.01.J and SAS version 8.01 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

The final analysis population comprised 304 patients (Table 1). Duration of follow-up time on the patients was median 4.57 months (range 0.10–52.57 months). Ninety-three patients (30.6%) had intrahepatic cholangiocarcinoma, 64 patients (21.1%) had extrahepatic cholangiocarcinoma and 147 patients (48.4%) had gallbladder cancer. Pathologic confirmation in cytological examination was 202 patients. Somewhat less than half (125 (41.1%)) of the patients received BSC and 179 (58.9%) took chemotherapy. Of the chemotherapy group, 30 patients (9.9%) were on 5-FU-based regimens, 20 patients (6.6%) took S-1, 58 patients (19.1%) took GEM, 27 patients (8.9%) took FAM and 44 patients (14.5%) were on CDDP-based regimens.

Response and Toxicity

Partial response was achieved in 15 of 179 chemotherapy patients (three with intrahepatic cholangiocarcinoma, two with extrahepatic cholangiocarcinoma and 10 with gallbladder cancer), but complete response was observed in no patients. Overall response rate was thus 8.4%. Stable disease was observed in 85 patients (47.5%) and progressive disease in 67 patients (37.4%). None (0%) of those on a 5 FU-based regimen showed a partial response, 11 (36.7%) remained

stable and 11 (36.7%) showed progressive disease. Three (15.0%) patients treated with S-1 showed a partial response, 10 (50.0%) remained stable and six (30.0%) showed progressive disease. Of those given GEM, four (6.9%) showed a partial response, 29 (50.0%) remained stable and 23 (39.7%) showed progressive disease. Three (11.1%) of the patients taking FAM showed a partial response, 11 (40.7%) remained stable and 13 (48.2%) showed progressive disease. Of those on a CDDP-based regimen, five (11.4%) showed a partial response, 24 (54.6%) remained stable and 11 (31.8%) showed progressive disease.

The data were also analyzed by tumor type. Three (6.0%) of the patients with intrahepatic cholangiocarcinoma showed a partial response, 24 (48.0%) remained stable, and 20 (40.0%) showed progressive disease. Two (5.7%) of the patients with extrahepatic cholangiocarcinoma showed a partial response, 17 (48.5%) remained stable and 12 (34.2%) showed progressive disease. Ten (10.6%) of the gallbladder cancer patients showed a partial response, 44 (46.8%) remained stable and 35 (37.2%) showed progressive disease.

As for toxicity, 40 (22.4%) had grade 3 nonhematological toxicities and 28 (15.6%) had grade 4 hematological toxicities. Among the patients taking 5-FU, five (16.7%) had grade 3 nonhematological toxicities. Of those taking S-1, 5 (25.0%) had grade 3 nonhematological toxicities. Of those taking GEM, 10 (17.2%) showed grade 3 nonhematological toxicities and two (3.5%) had grade 4 hematological toxicities. Two (7.4%) patients on the FAM regimen had grade 3 and six (22.2%) had grade 4 hematological toxicities. Among patients on a CDDP-based regimen, 18 (40.9%) had Grade 3 nonhematological toxicities and 20 (45.5%) had grade 4 hematological toxicities.

Survival

The number of deaths was 87 (69.6%) of the 125 BSC patients and 150 (83.8%) of the 179 chemotherapy patients. The median overall survival time was 3.12 months (95% CI 2.50–4.11) for BSC patients and 7.38 months (95% CI 6.25–8.77) for chemotherapy patients. Figure 2 shows the survival curves for the chemotherapy and the BSC groups. The difference in survival times was significant (logrank test P-value < 0.0001).

When the data for the chemotherapy group was analyzed by tumor type, the median overall survival time was 8.44 months (95% CI 5.15–11.2) for intrahepatic cholangiocarcinoma, 10.15 months (95% CI 5.38–13.7) for extrahepatic cholangiocarcinoma, and 6.50 months (95% CI 5.25–8.04) for gallbladder cancer. There was a statistically significant difference between extrahepatic cholangiocarcinoma and gallbladder cancer (logrank test P-value 0.029), but no difference between intrahepatic cholangiocarcinoma and gallbladder cancer (logrank test P-value 0.072). Gallbladder cancer patients died sooner than cholangiocarcinoma patients despite their better response to treatment.

Applying the Cox model yielded a hazard ratio for GEM of 0.50 (95% CI 0.35–0.72) and for CDDP-based regimens

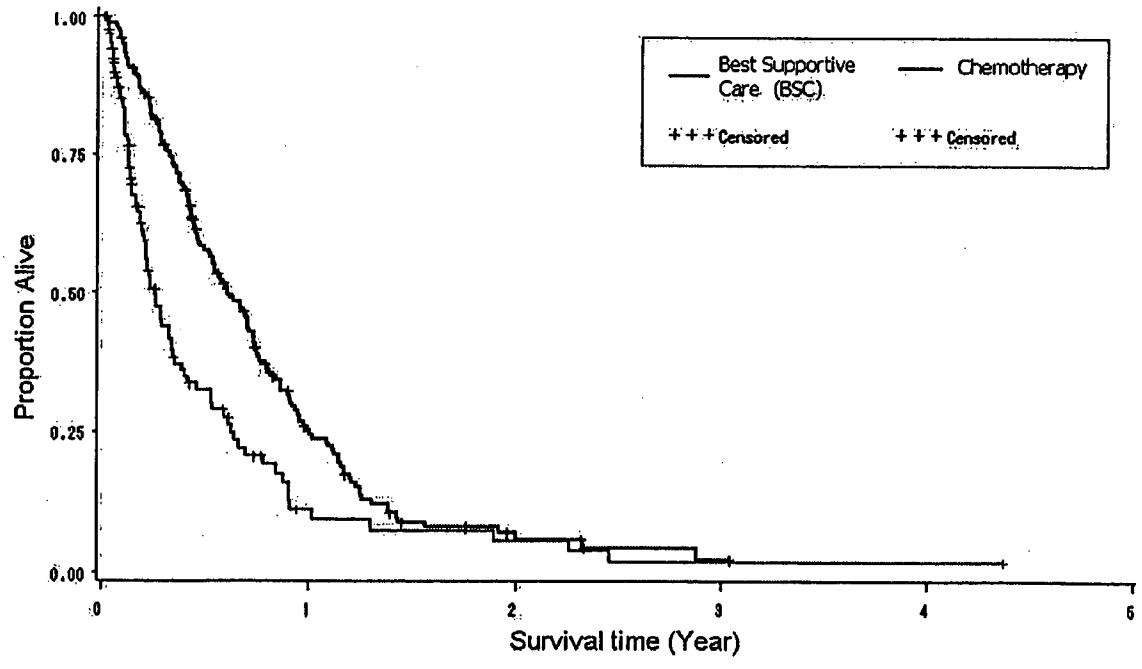

Figure 2. Black line: chemotherapy group. Gray line: best supportive care (BSC) group. +: censored observations.

Table 1. Patient characteristics

Variable		Chemotherapy ($n = 179$)										BSC		Total	
		5-FU		S-1		GEM		FAM		CDDP					
		$n = 30$ (9)		$n = 20$ (6)		$n = 58$ (19)		$n = 27$ (8)		$n = 44$ (14)		$n = 125$ (41)		$n = 304$	
		n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Sex	Female	17	(57)	7	(35)	28	(48)	13	(48)	23	(50)	49	(39)	137	(45)
	Male	13	(43)	13	(65)	30	(52)	14	(52)	21	(50)	76	(61)	167	(55)
Age	60 and over	19	(39)	12	(40)	42	(28)	17	(37)	20	(56)	109	(87)	219	(72)
	Less than 60	11	(61)	8	(60)	16	(62)	10	(63)	24	(44)	16	(13)	85	(28)
PS	0	13	(43)	9	(45)	27	(47)	13	(48)	18	(41)	25	(20)	105	(35)
	1	13	(43)	9	(45)	28	(48)	13	(48)	22	(50)	58	(46)	143	(47)
	2	4	(13)	2	(10)	2	(3)	1	(4)	3	(7)	28	(22)	40	(13)
	3	0	(0)	0	(0)	1	(2)	0	(0)	1	(2)	12	(10)	14	(5)
	4	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	2	(2)	2	(1)
Tumor	Intrahepatic	13	(43)	0	(0)	8	(14)	5	(19)	24	(54)	43	(34)	93	(31)
Type	Extrahepatic	7	(23)	2	(10)	16	(28)	3	(11)	7	(16)	29	(23)	64	(21)
	Gallbladder	10	(33)	18	(90)	34	(58)	19	(70)	13	(30)	53	(42)	147	(48)
CEA	10 and over	7	(23)	9	(45)	22	(38)	12	(44)	13	(30)	49	(39)	112	(37)
	Less than 10	23	(77)	11	(55)	36	(62)	15	(56)	31	(70)	76	(61)	192	(63)
CA19-9	1000 and over	11	(37)	7	(35)	21	(36)	6	(22)	11	(25)	54	(43)	110	(36)
	Less than 1000	19	(63)	13	(65)	37	(64)	21	(78)	33	(75)	71	(57)	194	(64)
Biliary drainage		11	(37)	6	(30)	19	(33)	10	(37)	9	(21)	66	(53)	121	(40)
Metastic site	Liver	7	(23)	14	(70)	27	(47)	10	(37)	19	(43)	46	(37)	123	(41)
	Peritoneum	4	(13)	2	(10)	7	(12)	4	(15)	6	(14)	14	(11)	37	(12)
	Lymph node	6	(20)	11	(55)	21	(36)	18	(67)	21	(48)	45	(36)	122	(40)
	Lung	3	(10)	2	(10)	3	(5)	3	(11)	5	(11)	13	(10)	29	(9)

BSC, best supportive care; 5-FU, 5-fluorouracil-based regimen; GEM, gemcitabine; FAM, 5-FU + doxorubicin + mitomycin C; CDDP, cisplatin-based regimen; CEA, carcinoembryonic antigen; CA, serum carbohydrate antigen.

of 0.51 (95% CI 0.34–0.76; Table 2). Figure 3 shows the survival curves for patients on each regimen and receiving BSC. The median time to treatment failure was 2.76 months (95% CI 1.74–4.40) for GEM patients and 5.52 months (95% CI 2.07–6.77) for CDDP-based regimens.

The adjusted hazard ratio in the Cox regression model for GEM was 0.53 (95% CI 0.34–0.82) and for CDDP-based regimens was 0.49 (95% CI 0.36–0.99). The adjusted hazard ratio in the Cox regression by modeling the propensity scores for GEM was 0.54 (95% CI 0.36–0.80) and for CDDP-based regimens 0.60 (95% CI 0.36–0.99; Table 3). Hazard ratio estimates obtained using the Cox regression and the propensity score were similar.

DISCUSSION

There is no standard chemotherapy for advanced biliary tract cancer. This study reports the impact of five types of chemotherapy on BTC compared with BSC. GEM was the most effective treatment, with a reduction in mortality of about 50%. GEM has already been shown to be an effective therapy for BTC in phase II trials (16–21). Response rates in GEM ranged from 8 to 36% and overall survival times from 6.3 to 16 months (44). The treatment is remarkably well tolerated, with very few patients (<5%) experiencing grade 4 hematologic toxicities. Hematologic adverse effects were infrequent and almost exclusively mild to moderate (44). A systematic review of the evidence on GEM from 13 single-arm phase II trials showed that GEM may be a reasonable option for treating BTC (45). Although GEM had been previously approved for solid tumors other than BTC (2), it was only approved for BTC in Japan in June of 2006.

CDDP-based regimens reduced mortality by 40%. However, we found a high frequency of grade 3 and 4 toxicities, making it unlikely that CDDP-based regimens can be used as standard therapy for BTC. Adverse events such as

Table 2. Median survival time and crude hazard ratio of treatment regimens and BSC

Treatment	Number (%)	MST (months) (95)% CI)	Hazard ratio (95)% CI)	*P*-value
BSC	125 (41)	3.12 (2.50–4.11)	Reference	—
Chemotherapy	179 (59)	7.38 (6.25–8.77)	0.55 (0.42–0.72)	<0.001
5-FU	30 (10)	7.23 (4.37–9.59)	0.65 (0.41–1.01)	0.058
S-1	20 (7)	5.95 (2.81–10.38)	0.71 (0.42–1.20)	0.209
GEM	58 (19)	8.05 (5.49–11.50)	0.50 (0.35–0.72)	0.0002
FAM	27 (9)	6.24 (4.93–7.66)	0.75 (0.48–1.18)	0.220
CDDP	44 (14)	8.51 (5.29–11.24)	0.51 (0.34–0.76)	0.001

MST, median survival time; CI, confidence interval.

inflammation of the biliary duct and hematological toxicity have been reported in other trials (25,46).

The combination of GEM with CDDP or other new platinum products such as oxaliplatin or with other anticancer drugs (47) might be an attractive option. A pooled analysis of the evidence from 112 single-arm phase II trials showed that GEM combined with platinum may be promising drugs for treating BTC (48). Results of the pooled analysis in phase II trials and our study are similar. In the UK, ABC trial-01 evaluates the role of CDDP in combination with GEM compared with GEM alone (49). A similar trial is ongoing in Japan. In future randomized trials, we recommend comparing GEM with a combination regimen of GEM and new platinum products such as oxaliplatin (34–36).

Although the result of S-1 in this study was not good, S-1 trials for regulatory approved had finished yet in Japan. The result of the trial was good. The response rate was 35% and

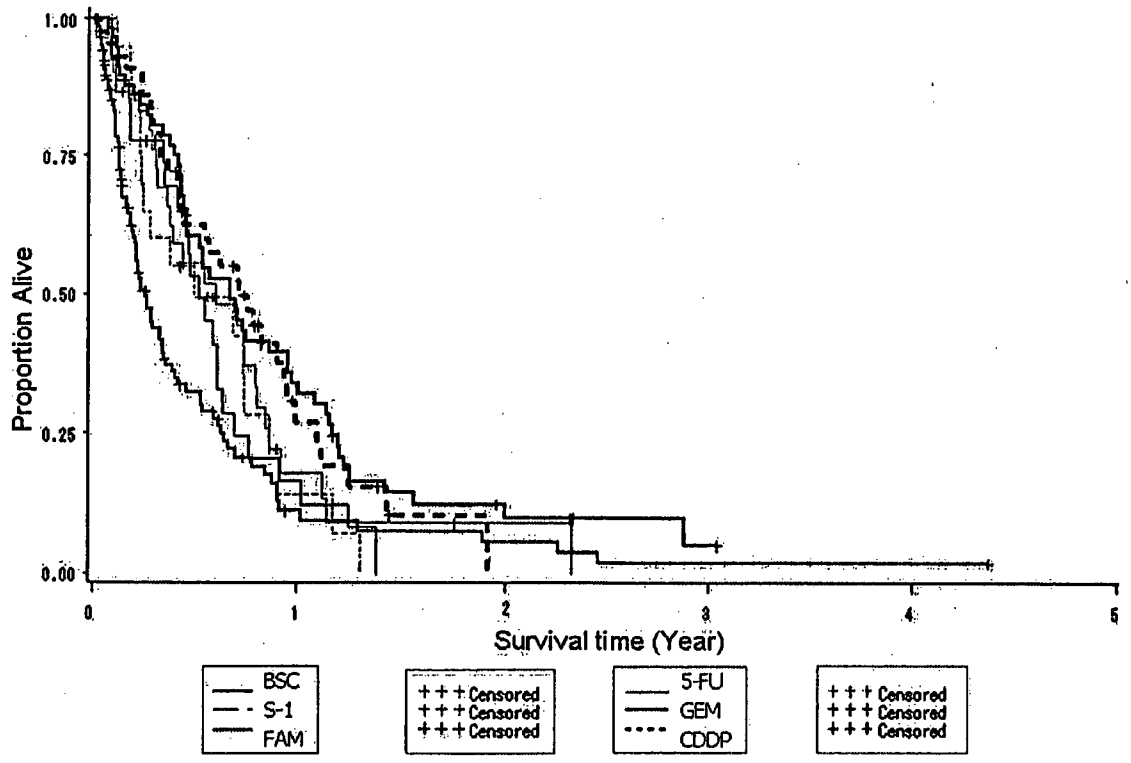

Figure 3. 5-FU: 5-fluorouracil-based regimen; GEM: gemcitabine; FAM: 5-FU + doxorubicin + mitomycin C; CDDP: cisplatin-based regimen. +: censored observations.

Table 3. Adjusted hazard ratios

Treatment	Multivariate analysis		Propensity score	
	Hazard ratio (95)% CI)	*P*-value	Hazard ratio (95)% CI)	*P*-value
BSC	Reference	—	Reference	—
Chemotherapy				
5-FU	0.81 (0.47–1.37)	0.436	0.74 (0.46–1.19)	0.210
S-1	0.70 (0.37–1.29)	0.258	0.86 (0.49–2.50)	0.593
GEM	0.53 (0.34–0.82)	0.004	0.54 (0.36–0.80)	0.002
FAM	0.76 (0.44–1.29)	0.315	0.91 (0.55–1.51)	0.719
CDDP	0.60 (0.36–0.99)	0.045	0.62 (0.38–0.99)	0.047

median survival time was 9.4 months (50). The GEM + S-1 trial has not been done yet. In future, S-1 or GEM + S-1 combined chemotherapy will be tested.

The limitations of this study are its retrospective nature and its nonrandomized design. There were some unbalances of baseline information in patient characteristics between the chemotherapy group and the BSC group. The proportion of patients with PS 2–3 or older age (over 60 years) in the BSC group was higher than in the chemotherapy group. We adjusted for known, measurable confounders through multivariate analysis and propensity score methods, but the study may still by limited by unmeasured confounders or information biases such as misclassification. We have no information for second- or third-line regimen each arm in this study. The second- or third-line treatment may affect the outcome of overall survival times. Our results should be supplemented by prospective trials using survival as the endpoint. The sample size was not large, and when the data was broken down by both disease and treatment regimen, some categories had few observations. For example, the S-1 treatment group included no patients with intrahepatic cholangiocarcinoma, and a much higher percentage of gallbladder cancer (90%) than the study group as a whole. This limits the interpretation of the results of the S-1 regimen. In the study, the low-dose CDDP regimen used a low dose under 10 mg. We thought that it should not classify within the class both this and another regimen with 80 mg/m^2 such as the CEA regimen. In addition, we consulted chemotherapy experts in a nonresearch group. Through this process, we decided that the classification of chemotherapies in the study and these regimens were separate. We did not classify low dose 5-FU plus CDDP regimen within the CDDP regimen and excluded the patients from the study. This classification may be subject to other opinions. We reviewed all patients for 3 years from September to December 2004 more than a year and a half from starting the treatment. Most lost cases were patients who moved to other hospitals on their own decision. We could not follow them in the study. This is a limitation in the study.

Survival times for patients with BTC can be affected by factors such as PS and tumor type. Gallbladder cancer patients had shorter survival times than patients with intrahepatic or extrahepatic cholangiocarcinoma (15,21,23), possibly reflecting the more aggressive biology of gallbladder cancer (25). Alternatively, the pattern could result from differing sensitivities to chemotherapy due to biological differences between biliary tract and gallbladder cancers. Such differences in sensitivity could not clearly explain the difference in survival between patients with biliary tract and gallbladder cancer in this study. Future randomized trials should employ stratified randomization by strong prognostic factors such as type of cancer, PS and presence of metastases.

Acknowledgment

This study was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare of Japan.

Conflict of interest statement

None declared.

References

1. De Groen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM.Biliary tract cancers. *New Engl J Med* 1999; 341:1368–78.
2. Okusaka T.Chemotherapy for biliary tract cancer in Japan. *Semin Oncol* 2002; 6 (Suppl 20):51–3.
3. Patel T. Worldwide trends in mortality from biliary tract malignancies. *BMC Cancer* 2002; 2:10.
4. Falkson G, MacIntyre JM, Moertel CG. Eastern Cooperative Oncology Group experience with chemotherapy for inoperable gallbladder and bile duct cancer. *Cancer* 1984; 54:965–9.
5. Glimelius B, Hoffman K, Sjoden PO, Jacobsson G, Sellstrom H, Enander LK, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 1996; 7:593–600.
6. Rao S, Cunningham D, Hawkins RE, Hill ME, Smith D, Daniel F, et al. Phase III study of 5FU, etoposide and leucovorin (FELV) compared to

epirubicin, cisplatin and 5FU (ECF) in previously untreated patients with advanced biliary cancer. *Br J Cancer* 2005; 92:1650–4.
7. Ishii H, Furuse J, Yonemoto N, Nagase M, Yoshino M, Sato T. Chemotherapy in the treatment of advanced gallbladder cancer. *Oncology* 2004; 66:138–42.
8. Kiba T, Nishimura T, Matsumoto S, Hatano E, Mori A, Yasumi S, et al. Single-agent gemcitabine for biliary tract cancers. Study outcomes and systematic review of the literature. *Oncology* 2006; 70:358–65.
9. Ducreux M, Rougier P, Fandi A, Clavero-Fabri MC, Villing AL, Fassone F, et al. Effective treatment of advanced biliary tract carcinoma using 5-fluorouracil continuous infusion with cisplatin. *Ann Oncol* 1998; 9:653–6.
10. Ducreux M, Van Cutsem E, Van Laethem JL, Gress TM, Jeziorski K, Rougier P, et al. EORTC Gastro Intestinal Tract Cancer Group: a randomised phase II trial of weekly high-dose 5-fluorouracil with and without folinic acid and cisplatin in patients with advanced biliary tract carcinoma: results of the 40955 EORTC trial. *Eur J Cancer* 2005; 41:398–403.
11. Cantore M, Mambrini A, Fiorentini G, Rabbi C, Zamagni D, Caudana R, et al. Phase II study of hepatic intraarterial epirubicin and cisplatin, with systemic 5-fluorouracil in patients with unresectable biliary tract tumors. *Cancer* 2005; 103:1402–7.
12. Ueno H, Okusaka T, Ikeda M, Takezako Y, Morizane C. Phase II study of S-1 in patients with advanced biliary tract cancer. *Br J Cancer* 2004; 91:1769–74.
13. Raderer M, Hejna MH, Valencak JB, Kornek GV, Weinlander GS, Bareck E, et al. Two consecutive phase II studies of 5-fluorouracil/leucovorin/mitomycin C and of gemcitabine in patients with advanced biliary cancer. *Oncology* 1999; 56:177–80.
14. Ikeda M, Okusaka T, Ueno H, Morizane C, Furuse J, Ishii H. A phase II trial of Uracil-tegafur (UFT) in patients with advanced biliary tract carcinoma. *Jpn J Clin Oncol* 2005; 35:439–43.
15. Furuse J, Okusaka T, Funakoshi A, Yamao K, Nagase M, Ishii H, et al. Early Phase II study of uracil-tegafur plus doxorubicin in patients with unresectable advanced biliary tract cancer. *Jpn J Clin Oncol* 2006; 36:552–6.
16. Penz M, Kornek GV, Raderer M, Ulrich-Pur H, Fiebiger W, Lenauer A, et al. Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. *Ann Oncol* 2001; 12:183–6.
17. Tsavaris N, Kosmas C, Gouveris P, Gennatas K, Polyzos A, Mouratidou D, et al. Weekly gemcitabine for the treatment of biliary tract and gallbladder cancer. *Invest New Drugs* 2004; 22:193–8.
18. Eng C, Ramanathan RK, Wong MK, Remick SC, Dai L, Wade-Oliver KT, et al. A Phase II trial of fixed dose rate gemcitabine in patients with advanced biliary tree carcinoma. *Am J Clin Oncol* 2004; 27:565–9.
19. Park JS, Oh SY, Kim SH, Kwon HC, Kim JS, Jin-Kim H, et al. Single-agent gemcitabine in the treatment of advanced biliary tract cancers: a phase II study. *Jpn J Clin Oncol* 2005; 35:68–73.
20. von Delius S, Lersch C, Schulte-Frohlinde E, Mayr M, Schmid RM, Eckel F. Phase II trial of weekly 24-hour infusion of gemcitabine in patients with advanced gallbladder and biliary tract carcinoma. *BMC Cancer* 2005; 5:61
21. Okusaka T, Ishii H, Funakoshi A, Yamao K, Ohkawa S, Saito S, et al. Phase II study of single-agent gemcitabine in patients with advanced biliary tract cancer. *Cancer Chemother Pharmac* 2006; 57:647–53.
22. Murad AM, Guimaraes RC, Aragao BC, Rodrigues VH, Scalabrini-Neto AO, Padua CA, et al. Phase II trial of the use of gemcitabine and 5-fluorouracil in the treatment of advanced pancreatic and biliary tract cancer. *Am J Clin Oncol* 2003; 26:151–4.
23. Knox JJ, Hedley D, Oza A, Siu LL, Pond GR, Moore MJ. Gemcitabine concurrent with continuous infusional 5-fluorouracil in advanced biliary cancers: a review of the Princess Margaret Hospital experience. *Ann Oncol* 2004; 15:770–4.
24. Hsu C, Shen YC, Yang CH, Yeh KH, Lu YS, Hsu CH, et al. Weekly gemcitabine plus 24-h infusion of high-dose 5-fluorouracil/leucovorin for locally advanced or metastatic carcinoma of the biliary tract. *Br J Cancer* 2004; 90:1715–19.
25. Alberts SR, Al-Khatib H, Mahoney MR, Burgart L, Cera PJ, Flynn PJ, et al. Gemcitabine, 5-fluorouracil, and leucovorin in advanced biliary tract and gallbladder carcinoma: a North Central Cancer Treatment Group phase II trial. *Cancer* 2005; 103:111–8.
26. Malik IA, Aziz Z, Zaidi SH, Sethuraman G. Gemcitabine and Cisplatin is a highly effective combination chemotherapy in patients with advanced cancer of the gallbladder. *Am J Clin Oncol* 2003; 26:174–7.
27. Doval DC, Sekhon JS, Gupta SK, Fuloria J, Shukla VK, Gupta S, et al. A phase II study of gemcitabine and cisplatin in chemotherapy-naive, unresectable gall bladder cancer. *Br J Cancer* 2004; 90:1516–20.
28. Thongprasert S, Napapan S, Charoentum C, Moonprakan S. Phase II study of gemcitabine and cisplatin as first-line chemotherapy in inoperable biliary tract carcinoma. *Ann Oncol* 2005; 16:279–81.
29. Lee GW, Kang JH, Kim HG, Lee JS, Lee JS, Jang JS. Combination chemotherapy with gemcitabine and cisplatin as first-line treatment for immunohistochemically proven cholangiocarcinoma. *Am J Clin Oncol* 2006; 29:127–31.
30. Kim ST, Park JO, Lee J, Lee KT, Lee JK, Choi SH, et al. A Phase II study of gemcitabine and cisplatin in advanced biliary tract cancer. *Cancer* 2006; 106:1339–46.
31. Kornek GV, Schuell B, Laengle F, Gruenberger T, Penz M, Karall K, et al. Mitomycin C in combination with capecitabine or biweekly high-dose gemcitabine in patients with advanced biliary tract cancer: a randomised phase II trial. *Ann Oncol* 2004; 15:478–83.
32. Knox JJ, Hedley D, Oza A, Feld R, Siu LL, Chen E, et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. *J Clin Oncol* 2005; 23:2332–8.
33. Cho JY, Paik YH, Chang YS, Lee SJ, Lee DK, Song SY, et al. Capecitabine combined with gemcitabine (CapGem) as first-line treatment in patients with advanced/metastatic biliary tract carcinoma. *Cancer* 2005; 104:2753–8.
34. Andre T, Tournigand C, Rosmorduc O, Provent S, Maindrault-Goebel F, Avenin D, et al. Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. *Ann Oncol* 2004; 15:1339–43.
35. Verderame F, Russo A, Di Leo R, Badalamenti G, Santangelo D, Cicero G, et al. Gemcitabine and oxaliplatin combination chemotherapy in advanced biliary tract cancers. *Ann Oncol* 2006; 17(Suppl 7): vii68–vii72.
36. Harder J, Riecken B, Kummer O, Lohrmann C, Otto F, Usadel H, et al. Outpatient chemotherapy with gemcitabine and oxaliplatin in patients with biliary tract cancer. *Br J Cancer* 2006; 95:848–52.
37. Androulakis N, Aravantinos G, Syrigos K, Polyzos A, Ziras N, Tselepatiotis E, et al. Oxaliplatin as first-line treatment in inoperable biliary tract carcinoma: a multicenter phase II study. *Oncology* 2006; 70:280–4.
38. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. Offset publication Geneva: World Health Organization, 1979.
39. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92: 205–16.
40. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 63:457–81.
41. Cox DR. Regression models and life-tables (with discussion). *J R Stat Soc (Ser B)* 1972; 34:187–220.
42. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; 70:41–55.
43. Robins JM, Mark SD, Newey WK. Estimating exposure effects by modelling the expectation of exposure conditional on confounders. *Biometrics* 1992; 48:479–95.
44. Scheithauer W. Review of gemcitabine in biliary tract carcinoma. *Semin Oncol* 2002; 29 (Suppl 20):40–5.
45. Dingle BH, Rumble RB, Brouwers MC. Cancer Care Ontario's Program in Evidence-Based Care's Gastrointestinal Cancer Disease Site Group: the role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer: a systematic review. *Can J Gastroenterol* 2005; 19:711–6.
46. Okada S, Ishii H, Nose H, Yoshimori M, Okusaka T, Aoki K, et al. A phase II study of cisplatin in patients with biliary tract carcinoma. *Oncology* 1994; 51:515–17.

47. Philip PA, Mahoney MR, Allmer C, Thomas J, Pitot HC, Kim G, et al. Phase II study of erlotinib in patients with advanced biliary cancer. *J Clin Oncol* 2006; 24:3069–74.
48. Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. *Br J Cancer* 2007; 96:896–902.
49. Valle JW, Wasan H, Johnson P, Bridgewater J, Maraveyas A E., Jones, et al. Gemcitabine, alone or in combination with cisplatin, in patients with advanced or metastatic cholangiocarcinoma (CC) and other biliary tract tumors: a multicenter, randomized, phase II (the UK ABC-01) study. ASCO 2006 Gastrointestinal Cancers Symposium abstract 98; Atlanta, GA, 2006.
50. Boku N, Okusaka T, Furuse J, Ohkawa S, Yamao K, Masumoto T, et al. Phase II study of S-1 in patients with unresectable or recurrent biliary tract cancer (BTC). *Ann Oncol* 2006; 17(Suppl): ix318.

● 消化器系の癌

胆道癌に対する化学療法

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要旨

胆道癌は切除不能な進行癌として発見されることが多いが，進行胆道癌に対する大規模な臨床試験はこれまでにほとんど行われておらず，標準的な非切除治療は確立していない．しかし，最近，胆道癌に対する抗がん剤の開発が活発化しており，幾つかの化学療法の臨床試験では有効性を示唆する結果も認められ始めている．本稿では，進行胆道癌に対する化学療法の現状と展望について，最新の話題を交えながら解説する．

はじめに

胆管癌や胆嚢癌などの胆道系の癌は比較的まれな疾患とされているが，日本や東南アジア，南米などでは罹患率が高いことが知られている．2004 年に我が国で胆道癌（肝外胆管癌，胆嚢癌，乳頭部癌）のために亡くなった患者の数は約 16,000 人で，がんによる死因の第 6 位となっている．胆道癌は早期発見が難しいことから，切除不能な進行癌の状態で発見されることが多く，たとえ切除されても再発しやすいため，胆道癌患者の予後は一般に不良である．日本胆道外科研究会の全国胆道癌登録調査報告によると，胆管癌，胆嚢癌患者の 5 年生存率は切除例ではそれぞれ 26％ と 42％ であり，進行例（Stage Ⅳ）では肝門部～上部胆管癌が 12％，中下部胆管癌が 15％ で，胆嚢癌

キーワード：胆管癌，胆嚢癌，胆道癌，化学療法，臨床試験

が9％であった[1].

進行胆道癌に対する治療成績を向上するためには有効な非切除治療の開発が必要不可欠であり，胆道癌患者の予後改善を求めて世界中でさまざまな試みが行われている．本稿では，その中で特に重要な役割を果たしてきた化学療法に関して，最新の話題を交えながら解説する．なお，肝内胆管癌は本邦では原発性肝癌に分類されているが，化学療法の分野では胆道癌と一緒に検討されることが多いため，本稿では肝内胆管癌も含めた集団を胆道癌と総称して解説することとする．

進行胆道癌に対する化学療法

胆道癌は進行癌で発見されることが多いため，臨床の現場では有効な非切除治療の開発が切望されている．しかし，この分野の研究は他の癌種と比べて遅れており，非切除治療の有効性はいまだに明らかにされていない．したがって，進行胆道癌患者に対して化学療法を行う際には，標準治療が確立していないことや緩和治療の選択肢も考えられることを十分に説明したうえで，患者本人の同意に基づき治療を行うことが大切である．

進行胆道癌に対して標準治療がいまだ確立していない背景には，胆道系の癌は多くの抗がん剤に対して抵抗性を示してきたという事実に加えて，以下に示すような胆道癌特有の問題点が化学療法の開発を妨げてきたものと思われる．

① 比較的まれな疾患である（特に臨床試験の盛んな欧米で）．

② 肝機能障害，閉塞性黄疸，胆管炎などを起しやすい．

③ 組織の採取や腫瘍径の計測が難しいことが多い．

④ 進行した状態で発見されやすいため，全身状態が不良なことが多い．

これらの理由から，臨床試験に適した患者を集めることが難しく，進行胆道癌に対する大規模な試験はこれまでほとんど行われてこなかった．

しかし最近では，胆道癌に対する抗がん剤の開発が活発化してきており，幾つかの化学療法に関しては有効性を示唆する結果も認められ始めている．以下，胆道癌に対するそれらの試みについて，国内外に

表1 国内で行われた進行胆道癌に対する臨床試験の成績

報告者	治療内容	患者数		奏効率 (%)	MST (月)	文献
		合計	胆嚢癌			
Takada ら	5－FU＋ADR＋MMC	42*	10	8	5.0	Hepatogastroenterology 1998
Okada ら	CDDP	13	6	7.7	5.5	Oncology 1994
Ikeda ら	UFT	19	8	5	8.8	Jpn J Clin Oncol 2005
Ueno ら	TS－1	19	16	21.1	8.3	Br J Cancer 2004
Boku ら	TS－1	41	20	35	9.4	ESMO 2006 [abstract]
Okusaka ら	ゲムシタビン	40	22	17.5	7.6	Cancer Chemother Pharmacol 2006
Morizane ら	CDDP＋EPI＋5－FU	37	32	19	5.8	Oncology 2003
Furuse ら	UFT＋ADR	24	13	12.5	7.6	Jpn J Clin Oncol 2006

MST：生存期間中央値，5－FU：5-フルオロウラシル，ADR：アドリアマイシン，MMC：マイトマイシンC，CDDP：シスプラチン，EPI：エピルビシン
*：膵癌患者28人を含む

分けて解説する．

日本における化学療法の現状

我が国で行われた進行胆道癌に対する臨床試験の結果を表1に示す．本邦では古くから，フルオロウラシル（5－FU）を中心とした化学療法が胆道癌に対して行われてきた．Takada らは，進行膵癌および進行胆道癌患者83人を，FAM（5－FU＋アドリアマイシン＋マイトマイシンC）群と緩和治療群とに分け無作為化比較試験を行ったが，FAM群の生存期間中央値は151日，緩和群の生存期間中央値は143日で有意差は認められなかった[2]．我々も，経口のフッ化ピリミジン系抗がん剤であるUFTの第Ⅱ相試験を進行胆道癌患者19人に対して行ったが，部分奏効（PR）が1人得られたのみ（奏効率5％）で，胆道癌に対するUFT単剤の有効性は低いと考えられた[3]．一方，Furuse らは，効果の増強を期待してUFTにアドリアマイシンを組み合わせた併用療法を24人の胆道癌患者に対して行い，奏効率12.5％（3/24）と，UFT単剤よりはやや良好な結果を報告している[4]．UFTとアドリアマイシンの併用に関しては，現在，さらに多数の患者の集積した後期第Ⅱ相試験が多施設共同で進行中である．

一方，新しい抗がん剤の臨床試験も現在我が国では活発に行われて

表2　進行胆道癌に対するゲムシタビン単剤療法の成績

報告者	治療内容	患者数		奏効率 (%)	MST (月)	文献
		合計	胆嚢癌			
Mezger ら	ゲムシタビン	13	4	8	NA	Onkologie 1998
Valencak ら	ゲムシタビン	24	8	17	6.8	Onkologie 1999
Valencak ら	ゲムシタビン（隔 週）	14	5	29	10.5	Onkologie 1999
Penz ら	ゲムシタビン（隔 週）	32	10	22	11.5	Ann Oncol 2001
Kubicka ら	ゲムシタビン	23	0	30	9.3	Hepatogastroenterology 2001
Gallardo ら	ゲムシタビン	26	26	36	7	Ann Oncol 2001
Gebbia ら	ゲムシタビン	18	12	22	8	J Clin Oncol 2001
Lin ら	ゲムシタビン	24	4	12.5	7.2	Chemotherapy 2003
Tsavaris ら	ゲムシタビン	30	14	30	14	Invest New Drugs 2004
Eng ら	ゲムシタビン（FDR）	15	9	0	4.6	Am J Clin Oncol 2004
Gelibter ら	ゲムシタビン（FDR）	40*	NA	0	9.2	Cancer 2005
Park ら	ゲムシタビン	23	8	26.1	13.1	Jpn J Clin Oncol 2005
Okusaka ら	ゲムシタビン	40	22	17.5	7.6	Cancer Chemother Pharmacol 2006

MST：生存期間中央値，FDR：定速静注法，NA：データなし
*：膵癌患者 27 人を含む

いる[5]．2006 年 6 月には，国内で行われた治験の結果に基づいて，胆道癌に対するゲムシタビン（商品名ジェムザール®）の保険適応が承認された．ゲムシタビンは代謝拮抗薬に分類される抗がん剤で，非小細胞肺癌や膵癌などに対して延命効果を有することが示されており，これらの癌を含むさまざまな癌種に対して世界中で広く使用されている．胆道癌に対しても近年幾つかの臨床試験で良好な成績が報告されており（表2），現在最も注目されている抗がん剤の1つである．本邦で行われた治験（第Ⅱ相試験）では，40 人の進行胆道癌患者（肝外胆管癌 12 人，胆嚢癌 22 人，乳頭部癌 6 人）が治療を受け，17.5％（7／40）の奏効率が認められた[6]．また，生存期間中央値は 7.6 ヵ月，1 年生存率は 25.0％ で，海外での報告と類似した結果であった．認められた主な副作用は，白血球減少や好中球減少，貧血などの骨髄抑制と食欲不振や悪心などの消化器症状，および肝機能障害であったが，重篤な副作用は少なく，他の癌種と同様に通院治療が多くの患者で可能であった．

ゲムシタビンに続いて胆道癌に対する保険適応の承認が待たれてい

るのが，経口のフッ化ピリミジン系抗がん剤の TS－1（商品名ティーエスワン®）である．TS－1 は日本で開発された抗がん剤で，胃癌や膵癌，非小細胞肺癌などさまざまな癌種に対する効果が報告されており，現在国内で広く使用されている．胆道癌に対しては，前期第Ⅱ相試験が国立がんセンター中央病院で行われ，19 人（肝外胆管癌 2 人，胆嚢癌 16 人，乳頭部癌 1 人）中 4 人に PR が認められたことが報告されている（奏効率 21.1％）[7]．また，生存期間中央値は 8.3 ヵ月，1 年生存率は 21.1％ と比較的良好な結果が認められた．骨髄抑制は軽度なことが多く，悪心，食欲不振，口内炎，下痢などの消化器症状と肝機能障害が主な副作用であったが一般に軽度で，ゲムシタビンと同様に外来での治療が可能であった．前期第Ⅱ相試験の結果を受けて行われた後期第Ⅱ相試験では，全国多施設で 40 人の進行胆道癌患者（肝外胆管癌 15 人，胆嚢癌 20 人，乳頭部癌 5 人）が登録され，治療を受けた．その結果前期第Ⅱ相試験を上回る 35％（14／40）の奏効率が認められ，生存期間中央値も 9.4 ヵ月と良好であった[8]．副作用は前期第Ⅱ相試験と同様に軽度のことが多かったが，1 人が治療関連と思われる敗血症のために死亡しており，状態が悪化しやすい胆道癌患者に化学療法を行う際は他癌種以上に注意が必要であることが示唆された．これらの前期・後期第Ⅱ相試験の結果を受けて，胆道癌に対する TS－1 の承認が申請され，現在審査が行われている．

海外における化学療法の現状

標準治療は確立していないものの，進行胆道癌に対して現在広く行われている治療は，NCCN のガイドライン[9]にも記載があるように 5－FU 系の抗がん剤を中心とした化学療法とゲムシタビンを中心とした化学療法である．

5－FU は胆道癌に対して古くから使用されてきた抗がん剤であるが，単剤での効果には限界がみられたことから，ロイコボリン，シスプラチン，マイトマイシンCなどさまざまな薬剤との併用療法が試みられてきた．これらの併用療法により比較的高い奏効率が報告されるようになったが，5－FU を中心とした併用化学療法が 5－FU 単剤療法よりも延命効果が優れているかはいまだ明らかにされていない．

Ducreux ら[10]は，進行胆道癌患者 58 人を対象に 5－FU＋ロイコボリン＋シスプラチン併用療法と 5－FU 単剤との無作為化比較第Ⅱ相試験を行い，奏効率は併用群 19％，単剤群 7.1％ で併用群に高い傾向にあるものの，副作用が増強し，生存期間の明らかな差は認められなかったことを報告している．最近は，5－FU の代わりに経口のフッ化ピリミジン系抗がん剤であるカペシタビンが使用される報告も増えており，カペシタビンにシスプラチンを併用したレジメンでは 42 人の胆道癌患者に対して 21.4％ の奏効率と 9.1ヵ月の生存期間中央値が報告されている[11]．

5－FU と比較すると，胆道癌に対してゲムシタビンが使用され始めたのは最近である．表2にこれまでに報告された胆道癌に対するゲムシタビン単剤の治療成績を示す．ゲムシタビン単剤の奏効率は 0～36％，生存期間中央値は 4.6～14ヵ月と試験によってばらつきはあるものの，既存の抗がん剤の成績と比較して良好な傾向にある．さらに最近では，より強い抗腫瘍効果を目指して，ゲムシタビンと他の薬剤との併用療法も積極的に試みられるようになっている．その中でもゲムシタビン＋シスプラチン，ゲムシタビン＋オキサリプラチン，ゲムシタビン＋カペシタビンなどのレジメンは 30％ 前後の高い奏効率と8ヵ月を超す良好な生存期間中央値が報告されており，今後の進展が期待されている（表3）．

ゲムシタビンを中心とした化学療法は，今後進行胆道癌に対する標準治療になる可能性を秘めた治療であるが，現時点では 5－FU を中心とした化学療法と同様に胆道癌患者に対する延命効果は証明されていない．英国では無作為化比較第Ⅱ相試験でゲムシタビン＋シスプラチン併用療法の無増悪生存期間がゲムシタビン単剤よりも優れていたことが報告されており[12]，その結果を受けて現在，ゲムシタビン vs. ゲムシタビン＋シスプラチンの第Ⅲ相試験が進行中である．

また，最近では分子標的薬剤の臨床試験も活発に行われている．Philip らは，進行胆道癌患者 42 人（肝内胆管癌 15 人，肝外胆管癌 9 人，胆嚢癌 16 人，分類不能2人）に対して上皮成長因子受容体のチロシンキナーゼ阻害薬である erlotinib の投与を行い，抗腫瘍効果の判定が可能であった 40 人中3人（8％）に PR，17 人（43％）に

表3 進行胆道癌に対するゲムシタビンを中心とした併用療法の成績

報告者	治療内容	患者数		奏効率 (%)	MST (月)	文献
		合計	胆嚢癌			
Alberts ら	GEM＋5－FU＋LV	42	14	9.5	9.7	Cancer 2004
Cho ら	GEM＋カペシタビン	44	7	32	14	Cancer 2005
Knox ら	GEM＋カペシタビン	45	22	31	14	J Clin Oncol 2005
Thongprasert ら	GEM＋シスプラチン	43	1	27.5	8.3	Ann Oncol 2005
Kim ら	GEM＋シスプラチン	29	10	34.5	11	Cancer 2005
Giuliani ら	GEM＋シスプラチン	38	10	32	8+	Ann Oncol 2006
Andre ら	GEM＋オキサリプラチン	33	11	36	15.4	Ann Oncol 2004
Verderame ら	GEM＋オキサリプラチン	24	9	50	12	Ann Oncol 2006
Harder ら	GEM＋オキサリプラチン	31	10	26	11	Br J Cancer 2006

MST：生存期間中央値，GEM：ゲムシタビン，5－FU：5-フルオロウラシル，LV：ロイコボリン

不変（SD）が認められたことを報告している[13]．全症例（42人）の生存期間中央値は7.5ヵ月であった．一方，上皮成長因子受容体のErbB－1とErbB－2（HER2）の双方を阻害するチロシンキナーゼ阻害薬であるlapatinibに関しては，2006年の米国臨床腫瘍学会（ASCO）で進行胆道癌に対する第Ⅱ相試験の結果が報告されたが，17人中1人もPRは認められず（SD：26％），期待された結果は得られなかった[14]．そのほか，血管新生阻害薬のbevacizumabやマルチキナーゼ阻害薬のsorafenibなどが胆道癌に対して現在試みられている．

おわりに

胆道癌は進行癌が多いにもかかわらず，これまで化学療法を含む非切除治療の開発が遅れていた．しかし近年，ゲムシタビンを始めとする新しい薬剤を評価する試みが活発化しており，一部では大規模な臨床試験が計画・実施され始めている．我が国には胆道癌患者が比較的多いことから，胆道癌に対する標準治療の確立に役立つような大規模かつ質の高い臨床試験を多施設共同で行っていくことが今後必要である．

文　　献

1) Nagakawa T, et al: Biliary tract cancer treatment: results from the Biliary Tract Cancer Statistics Registry in Japan. J Hepatobiliary Pancreat Surg 9 (5): 569–575, 2002.
2) Takada T, et al: Prospective randomized trial of 5–fluorouracil, doxorubicin, and mitomycin C for non–resectable pancreatic and biliary carcinoma: multicenter randomized trial. Hepatogastroenterology 45 (24): 2020–2026, 1998.
3) Ikeda M, et al: A phase II trial of Uracil–tegafur (UFT) in patients with advanced biliary tract carcinoma. Jpn J Clin Oncol 35 (8): 439–443, 2005.
4) Furuse J, et al: Early phase II study of uracil–tegafur plus doxorubicin in patients with unresectable advanced biliary tract cancer. Jpn J Clin Oncol 36 (9): 552–556, 2006.
5) Okusaka T: Chemotherapy for biliary tract cancer in Japan. Semin Oncol 29 (6 Suppl 20): 51–53, 2002.
6) Okusaka T, et al: Phase II study of single–agent gemcitabine in patients with advanced biliary tract cancer. Cancer Chemother Pharmacol 57 (5): 647–653, 2006.
7) Ueno H, et al: Phase II study of S–1 in patients with advanced biliary tract cancer. Br J Cancer 91 (10): 1769–1774, 2004.
8) Boku N, et al: Phase II study of S–1 in patients with unresectable or recurrent biliary tract cancer [abstract]. 2006 European Society for Medical Oncology (ESMO).
9) http://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf
10) Ducreux M, et al: EORTC Gastro Intestinal Tract Cancer Group. A randomised phase II trial of weekly high–dose 5–fluorouracil with and without folinic acid and cisplatin in patients with advanced biliary tract carcinoma: results of the 40955 EORTC trial. Eur J Cancer 41 (3): 398–403, 2005.
11) Kim T W, et al: Phase II study of capecitabine plus cisplatin as first–line chemotherapy in advanced biliary cancer. Ann Oncol 14 (7): 1115–1120, 2003.
12) Valle J W, et al: Gemcitabine, alone or in combination with cisplatin, in patients with advanced or metastatic cholangiocarcinomas and other biliary tract tumours: a multicenter, randomised phase II study [abstract]. 2006 Gastrointestinal Cancers Symposium.
13) Philip P A, et al: Phase II study of erlotinib in patients with advanced biliary cancer. J Clin Oncol 24 (19): 3069–3074, 2006.
14) Ramanathan R K, et al: Phase II study of Lapatinib, a dual inhibitor of epidermal growth factor receptor tyrosine kinase 1 and 2 (Her2/Neu) in patients with advanced biliary tree cancer or hepatocellular cancer. A California Consortium Trial [abstract]. 2006 ASCO Annual Meeting.

Chemotherapy for Biliary Tract Cancer

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切除不能進行胆道癌に対するchemotherapy

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索引用語：胆道癌，胆管癌，化学療法

1 はじめに

胆道癌(胆嚢癌，肝外胆管癌，乳頭部癌)の年間死亡者数は年々増加傾向であり，現在本邦の癌による死亡の第6位である．現時点では切除術が唯一の根治療法であるが，自覚症状が出現しにくいことから進行癌の状態で発見されることが多く，また切除後の再発も高率である．進行胆道癌に対する標準治療は確立しておらず，各種ガイドラインでは局所進行例，遠隔転移例とも臨床試験への参加が重要な選択肢として挙げられている．日常臨床の現場では遠隔転移を有する例については全身化学療法もしくは緩和ケアが選択肢に挙がる．遠隔転移のない局所進行例では放射線療法(体外照射もしくは腔内照射)，光力学療法(photodynamic therapy)，化学放射線療法，全身化学療法，緩和ケアのいずれかが，選択肢として挙げられる．現在局所進行例に対してどのモダリティが最も優れているかについてはわかっていないため，日常診療における局所進行例に対する治療方針のコンセンサスは得られていない．本稿では進行胆道癌に対する全身化学療法について現時点で報告されている研究結果をもとに，国内外の現状について述べる．

2 進行胆道癌に対する全身化学療法 —単剤療法—

現在までに胆道癌領域でなされた臨床試験は対照群のない試験や，小規模な比較試験のみで大規模な第Ⅲ相試験の報告はない．表1に現在までに報告された単剤での治療成績を示す[1~15]．単剤ではフッ化ピリミジン系薬剤やゲムシタビンにおいて比較的良好な成績が報告されている．

1．ゲムシタビン(ジェムザール®)

ゲムシタビンは代謝拮抗剤に分類される抗癌剤で，細胞内で三リン酸化物に代謝され，DNAの合成を阻害する．また，三リン酸化物濃度は細胞内で長時間維持され，固形癌に対して強い殺細胞作用を示す．ゲムシタビン

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