

Guidelines for chemotherapy of biliary tract and ampullary carcinomas

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Abstract

Few randomized controlled trials (RCTs) with large numbers of patients have been conducted to date in patients with biliary tract cancer, and standard chemotherapy has not been established yet. In this article we review previous studies and clinical trials regarding chemotherapy for unresectable biliary tract cancer, and we present guidelines for the appropriate use of chemotherapy in patients with biliary tract cancer. According to an RCT comparing chemotherapy and best supportive care for these patients, survival was significantly longer and quality of life was significantly better in the chemotherapy group than in the control group. Thus, chemotherapy for patients with biliary tract cancer seems to be a significant treatment of choice. However, chemotherapy for patients with biliary tract cancer should be indicated for those with unresectable, locally advanced disease or distant metastasis, or for those with recurrence after resection. That is why making the diagnosis of unresectable disease should be done with greatest care. As a rule, pathological diagnosis, including cytology or histopathological diagnosis, is preferable. Chemotherapy is recommended in patients with a good general condition, because in patients with general deterioration, such as those with a performance status of 2 or 3 or those with insufficient biliary decompression, the benefit of chemotherapy is limited. As chemotherapy for unresectable biliary tract cancer, the use of gemcitabine or tegafur/gimeracil/oteracil potassium is recommended. As postoperative adjuvant chemotherapy, no effective adjuvant therapy has been established at the present time. It is recommended that further clinical trials, especially large multi-institutional RCTs (phase III studies) using novel agents such as gemcitabine should be performed as soon as possible in order to establish a standard treatment.

Key words Biliary tract cancer · Systemic chemotherapy · Adjuvant chemotherapy · Guidelines

Introduction

Chemotherapy in patients with biliary tract cancer is indicated in those with unresectable advanced cancer and patients with recurrence after resection. However, no standard chemotherapy for biliary tract cancer has yet been established, because few randomized controlled trials (RCTs) with large numbers of patients have been conducted to date. There are a number of studies regarding chemotherapy for biliary tract cancer, but many of these studies were prospective clinical trials with small numbers of patients, corresponding to phase II studies, or retrospective studies, so high-level evidence in this area is limited. According to the “Classification of Biliary Tract Carcinoma”, bile duct cancer, gallbladder cancer, and ampullary cancer are classified as biliary tract cancer, and there are some clinical trials and articles in which treatment results that include those in intrahepatic bile duct cancer are also reported. If clinical trials are conducted for individual diseases separately, difficulties are encountered in view of efficiency and implementation, and so far, clinical trials of chemotherapy have been carried out only for biliary tract cancer in general. However, because treatment policy, sensitivity to chemotherapy, and prognosis differ widely from disease to disease, the treatment results of chemotherapy in biliary tract cancer should be evaluated on the basis of a full understanding of individual background factors.

In the present guidelines, chemotherapy for unresectable biliary tract cancer and postoperative adjuvant

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chemotherapy has been described based on results from clinical trials and retrospective studies performed up to now. In order that effective chemotherapy for biliary tract cancer may be developed, active implementation of clinical trials is recommended. Also, large multi-institutional RCTs (phase III) should be conducted to establish standard treatment as soon as possible.

The only procedure in biliary cancer that confers a cure is curative surgical resection, so a diagnosis of incurability should be made with caution. Lest the cancer be benign, surgical treatment should be administered as a rule only after pathological diagnosis (such as cytological and histological diagnoses) has been made. The chemotherapy described in these Guidelines is concerned with adenocarcinoma, which has the highest frequency of occurrence, so pertinent literature should be referred to in selecting treatment methods for other specific pathological types of cancer. In these Guidelines, clinical questions (CQs) are posed, with responses in the form of recommendations (grades of the recommendations are defined in Table 1¹). Also, levels of evidence are given (in parentheses) for findings in reference citations (see definitions of levels in Table 2¹).

CQ 1 Does chemotherapy have any benefits in patients with unresectable biliary tract cancer?

Chemotherapy is recommended in patients with good general physical condition (recommendation C1).

To assess the efficacy of chemotherapy in achieving prolonged survival in biliary tract cancer, verification is necessary by comparing it with supportive treatment

Table 1. Strength of recommendations¹

A, Strongly recommend performing the clinical action
B, Recommend performing the clinical action
C1, The clinical action may be considered although there is a lack of high-level scientific evidence for its use. May be useful
C2, Clinical action not definitively recommended because of insufficient scientific evidence. Evidence insufficient to support or deny usefulness
D, Recommend not performing the clinical action

Table 2. Levels of evidence¹

Level I	Systematic review/meta-analysis
Level II	One or more randomized clinical trials
Level III	Nonrandomized controlled trials
Level IV	Analytic epidemiology (cohort studies and case-control studies)
Level V	Descriptive study (case reports and case-series studies)
Level VI	Opinions of expert panels and individual experts not based on patient's data

alone. To date, only two small RCTs (level II) have been published.^{2,3}

An RCT on chemotherapy and supportive treatment was conducted in patients with unresectable pancreas cancer and biliary tract cancer.² In this study, fluorouracil (5-FU) + leucovorin or 5-FU + leucovorin + etoposide were used for chemotherapy. For all the patients, significantly prolonged survival was observed in the group who received chemotherapy (median survival time [MST], 6.0 months) compared with the group who received supportive treatment alone (MST, 2.5 months). However, due to the small number of patients with biliary tract cancer (37 patients), no significant difference was established between the groups (chemotherapy group MST, 6.5 months; supportive treatment group, 2.5 months; $P = 0.1$). The rate of improvement in quality of life (QOL) was also examined in this trial, and a significant difference was found in the chemotherapy group compared with the supportive treatment group ($P < 0.01$); an improvement of 36% was observed in the chemotherapy group (pancreas cancer, 38%; biliary tract cancer, 33%) and an improvement of 10% (pancreas cancer, 13%; biliary tract cancer, 5%) was shown in the supportive treatment group.

The other small RCT³ was conducted in Japan, comparing chemotherapy with 5-FU + doxorubicin + mitomycin C (FAM) and palliative treatment, such as bypass, in patients with unresectable pancreatic cancer, gallbladder cancer, and bile duct cancer. No significant improvement in prognosis was achieved in either group, but in the patients with gallbladder cancer, a good prognosis was achieved in the chemotherapy group (level II).

A retrospective analysis comparing chemotherapy and supportive treatment in patients with gallbladder cancer was carried out. No survival benefit owing to chemotherapy was observed in patients with a performance status of 2, while prolonged survival in the chemotherapy group was observed in patients with a performance status of 0 or 1⁴ (level IV).

Concerning the efficacy of chemotherapy for unresectable biliary tract cancer, no evidence based on an RCT with a large number of patients is available, but there are reports demonstrating the efficacy of chemotherapy in achieving improved QOL and prolonged survival. Thus, the strength of the recommendation for chemotherapy was determined as C1.²⁻⁴

Table 3. Systemic chemotherapy with single agents for biliary tract cancer

Agent	Response			Study design	Evidence level	Author	Year	Reference
	<i>n</i>	rate	MST (months)					
Fluorouracil								
5-FU	18	0%	—	RCT	Level II	Takada	1994	19
5-FU/LV/HU	30	30%	8.0	Cohort study	Level III	Gebbia	1996	22
5-FU/ α -IFN	32	34%	12.0	Cohort study	Level III	Patt	1996	23
5-FU/LV	18	33%	7.0	Cohort study	Level III	Chen	1998	24
5-FU/LV	28	32%	6.0	Cohort study	Level III	Choi	2000	25
5-FU/FA	30	7%	14.8	Cohort study	Level III	Malik	2003	26
UFT/LV	13	0%	6.5	Cohort study	Level III	Mani	1999	5
UFT/LV	16	0%	4.5	Cohort study	Level III	Chen	2003	6
Capecitabine	26	19%	CC, 8.1; GB, 9.9	Cohort study	Level III	Patt	2004	27
S-1	19	21%	8.3	Cohort study	Level III	Ueno	2004	28
UFT	19	5%	8.8	Cohort study	Level III	Ikeda	2005	7
S-1	40	30%	9.4	Cohort study	Level III	Furuse	in press	9
Taxanes								
Paclitaxel	15	0%	—	Cohort study	Level III	Jones	1996	29
Docetaxel	16	0%	—	Cohort study	Level III	Pazdur	1999	30
Docetaxel	24	20%	8.0	Cohort study	Level III	Papakostas	2001	31
Gemcitabine								
Gemcitabine (800 mg/m ²)	30	30%	14.0	Cohort study	Level III	Tsavaris	2004	32
Gemcitabine (1000 mg/m ²)	25	36%	7.0	Cohort study	Level III	Gallardo	2001	33
Gemcitabine (1000 mg/m ²)	24	13%	7.2	Cohort study	Level III	Lin	2003	34
Gemcitabine (1000 mg/m ²)	40	18%	7.6	Cohort study	Level III	Okusaka	2006	8
Gemcitabine (1200 mg/m ²)	19	16%	6.5	Cohort study	Level III	Raderer	1999	35
Gemcitabine (1500 mg/m ²)	15	0%	4.6	Cohort study	Level III	Eng	2004	36
Gemcitabine (2200 mg/m ²)	32	22%	11.5	Cohort study	Level III	Penz	2001	27
Others								
Mitomycin C	30	10%	4.5	Cohort study	Level III	Taal	1993	38
Cisplatin	13	8%	5.5	Cohort study	Level III	Okada	1994	39
Irinotecan	36	8%	6.1	Cohort study	Level III	Alberts	2002	40
Erlotinib	42	8%	7.5	Cohort study	Level III	Philip	2006	14

MST, median survival time; 5-FU, 5-fluorouracil; IFN, interferon; LV, leuovorin; FA, folinic acid; HU, hydroxyurea; CC, cholangiocarcinoma; GB gallbladder

The use of chemotherapy for biliary tract cancer should be limited to patients with unresectable, locally advanced disease and distant metastasis, or those with recurrence after resection. Chemotherapy is recommended in patients with a good general condition. However, in patients with general deterioration (performance status of 2 or 3) or those with insufficient biliary decompression, the benefit of chemotherapy is small, so care should be taken in considering its indications. In these patients, palliative treatment targeting the maintenance of QOL should be administered, including pain control and the placement of stents in the bile duct.

CQ 2 What is a recommended chemotherapy regimen?

As chemotherapy for unresectable advanced biliary tract carcinoma, gemcitabine or tegafur/gimeracil/oteracil potassium is recommended (recommendation C1).

Table 3 shows the results of systemic chemotherapy with a single agent for biliary tract cancer. The single use of fluoropyrimidines such as 5-FU, or a combination of 5-FU with interferon, leucovorin, or hydroxyurea as biochemical modulators, was often used for advanced biliary tract cancer. A favorable response rate of more than 30% has been reported with the combined use of a single agent with these modulators, but no difference was observed in MST, which ranged from 7 to 12 months, in studies in patients undergoing chemotherapy for unresectable biliary tract cancer, compared with patients who received best supportive care (level III). In Japan, uracil-tegafur (UFT) is approved by the Ministry of Health, Labor, and Welfare for biliary tract cancer. However, regimens of UFT alone or UFT plus leucovorin were reported to have objective responses of 5% and 0%, respectively, and more than 60% patients were evaluated as having progressive disease in these regimen. Therefore, UFT should not be used alone for biliary tract cancer (level III).

Table 4. Combination chemotherapy for biliary tract cancer

Regimen	<i>n</i>	Response rate	MST (months)	Study design	Evidence level	Author	Year	Reference
5-FU-based								
5-FU/ADM/MMC (FAM)	14	29%	8.5	Cohort study	Level III	Harvey	1984	41
EPI/MTX/5-FU/LV	17	0%	9.0	Cohort study	Level III	Kajanti	1994	42
5-FU/LV/MMC	20	25%	9.5	Cohort study	Level III	Raderer	1999	35
MMC/5-FU/LV	19	26%	6.0	Cohort study	Level III	Chen	2001	43
Platinum-based								
EPI/CDDP/5-FU (ECF)	20	40%	11.0	Cohort study	Level III	Ellis	1995	44
CDDP/EPI/5-FU (CEF)	37	19%	5.9	Cohort study	Level III	Morizane	2003	45
5-FU/CDDP	25	24%	10.0	Cohort study	Level III	Ducreux	1998	46
5-FU/CDDP/LV	29	34%	9.5	Cohort study	Level III	Taieb	2002	47
Capecitabine/CDDP	42	21%	9.1	Cohort study	Level III	Kim TW	2003	48
CDDP/IFN/DXR/5-FU (PIAF)	38	21%	14.0	Cohort study	Level III	Patt	2001	49
EPI/CDDP/UFT/LV	40	23%	7.9	Cohort study	Level III	Park KH	2005	50
EPI/CDDP/capecitabine	43	40%	8.0	Cohort study	Level III	Park SH	2006	51
5-FU/LV/Carboplatin	14	21%	5.0	Cohort study	Level III	Sanz-Altamira	1998	52
5-FU/LV/Oxaliplatin (FOLFOX)	16	19%	9.5	Cohort study	Level III	Nehls	2002	53
Gemcitabine-based								
Gemcitabine/Docetaxel	43	9%	11.0	Cohort study	Level III	Kuhn	2002	54
Gemcitabine/5-FU	27	33%	5.3	Cohort study	Level III	Knox	2004	55
Gemcitabine/5-FU/LV	42	12%	4.7	Cohort study	Level III	Hsu	2004	56
Gemcitabine/5-FU/LV	42	12%	9.7	Cohort study	Level III	Alberts	2005	57
Gemcitabine/CDDP	30	38%	4.6	Cohort study	Level III	Doval	2004	10
Gemcitabine/CDDP	40	28%	8.4	Cohort study	Level III	Thongprasert	2005	11
Gemcitabine/CDDP	29	35%	11.0	Cohort study	Level III	Kim ST	2006	12
Gemcitabine/CDDP	27	33%	10.0	Cohort study	Level III	Park BK	2006	13
Gemcitabine/oxaliplatin	33	33%	15.4	Cohort study	Level III	Andre	2004	58
Gemcitabine/capecitabine	45	31%	14.0	Cohort study	Level III	Knox	2005	16
Gemcitabine/capecitabine	45	32%	14.0	Cohort study	Level III	Cho	2005	59

MST, median survival time; MTX, methotrexate; MMC, Mitomycin C; 5-FU, 5-fluorouracil; LV, leucovorin; IFN, interferon

Side memo

In Japan, none of the above modulators are approved by the Ministry of Health, Labour, and Welfare for use as chemotherapeutic drugs in biliary tract cancer.

Since 1999, clinical trials have been conducted with gemcitabine. Although methods of administration are different, relatively good results are reported (Table 3). A clinical trial (phase II) was carried out with gemcitabine alone in Japan.⁸ A response rate of 17.5% (95% confidence intervals [CI], 7.3%–32.8%), and an MST of 7.6 months was achieved with the standard dosage, which was 1000 mg/m² as a 30-min intravenous infusion weekly, given for 3 consecutive weeks, followed by a week of rest, the results being roughly similar to those of reports from abroad. Toxicity inducing myelosuppression, such as leucopenia, as well as nausea and anorexia, was mainly observed, but tolerance was good. Based on these results, gemcitabine was approved by the Ministry of Health, Labour, and Welfare, in June, 2006, for use in biliary tract cancer (level III).

A clinical trial of tegafur/ gimeracil/oteracil potassium (S-1), which is an oral anticancer drug that consists of tegafur (FT) as a prodrug of 5-FU, 5-chloro-2, 4-dihydropyridine (CDHP), and potassium oxonate (Oxo), was conducted in Japan. S-1 was orally administered at a dose of 80 mg/m² per day for 28 days, followed by 14 days of rest. In a late phase II trial, a favorable result was reported, with a success rate of 35% and MST of 9.4 months in 40 patients. Because of this result, insurance coverage for the use of this agent for biliary tract cancer was endorsed in August, 2007 (level III).

There are also some reports of the use of mitomycin C, cisplatin, taxanes, and irinotecan (CPT-11) (Table 3), but no satisfactory result has been achieved (level III).

For biliary tract cancer, there is a limitation in treatment effects brought about by chemotherapy with the use of a single agent, so many modalities of combination chemotherapy have been carried out (Table 4). Compared with single-agent chemotherapy, the response rate of combination chemotherapy is generally high and the survival period is also inclined to be long. Although a regimen of a combination of 5-FU, anthracycline, and platinum has often been employed, no standard regimen has been established. An attempt at a regimen focusing

Table 5. Randomized clinical trials for unresectable biliary tract cancer

	<i>n</i>	Response rate	MST (months) GB/BD	<i>P</i> value	Study design	Evidence level	Author (year)	Reference
1) Oral 5-FU	30	10%	4.9/6.1	NS	RCT	Level II	Falkson (1984)	60
2) Oral 5-FU + Stz	26	7.7%	3.3/2.8					
3) Oral 5-FU + MeCCNU	31	9.7%	2.3/1.9					
1) Modified FAM	35 (18) ^a	4%	6.2 ^b	NS	RCT	Level II	Takada (1994)	19
2) 5-FU	36 (18) ^a	0%	6.0 ^b					
1) 5-FU + LV or FELV	47 (18) ^a	11%	6.5 (6.5) ^b	0.1	RCT	Level II	Glimelius (1996)	2
2) BSC	43 (19) ^a	—	2.5 (2.5) ^b					
1) Modified FAM	14	—	5.2/4.1	NS	RCT	Level II	Takada (1998)	3
2) Palliative surgery	17	—	2.4/7.7					
1) MMC + gemcitabine	25	20%	6.7	—	RCT	Level II	Kornek (2004)	61
2) MMC + capecitabine	26	31%	9.3					
1) 5-FU	29	—	5.0	—	RCT	Level II	Ducreux (2005)	62
2) 5-FU + FA + cisplatin	29	—	8.0					
1) ECF	27	—	9.0	0.72	RCT	Level II	Rao (2005)	63
2) FELV	27	—	12.0					

MST, median survival time; GB, gallbladder; BD, bile duct; Stz, streptozotocin; MeCCNU, methyl-CCNU; LV, levofofinic acid (lecovorin); BSC, best supportive care; MMC, mitomycin C; FA, folinic acid; FAM, 5-FU + adriamycin + MMC; FELV, 5-FU + etoposide + leucovorin; ECF, epirubicin + cisplatin + 5-FU

^aThe total number of patients in the study, including those with pancreatic cancer; numbers in parentheses, numbers of patients with biliary tract cancer

^bThe median overall survival time in all patients in the study, including those with pancreatic cancer; numbers in parentheses, median overall survival times in patients with biliary tract cancer

on the use of gemcitabine is currently being made and a favorable result has been achieved, with the response rate being 21%–48% and MST, 4.6–11.0 months in patients treated with gemcitabine + cisplatin^{10–13} (level III). Currently, a large controlled trial comparing gemcitabine alone and gemcitabine + cisplatin (CDDP) is being conducted chiefly by an English group and it is drawing attention. Also, therapeutic drugs targeting molecular biological characteristics (molecular targeting therapy) are now under development. In view of a report suggesting the strong expression of epithelial growth factor receptor (EGFR) in biliary tract cancer, a phase II trial using erlotinib, which is an EGFR-inhibiting drug, is being carried out.¹⁴

In biliary tract cancer, treatment results differ widely depending upon the site of the cancer. In clinical trials, patients' backgrounds, particularly the proportions of those with gallbladder cancer, bile duct cancer, and ampullary cancer, have a big impact on treatment results, such as the survival period.^{7,15,16} In a phase II study of gemcitabine + capecitabine, the MST in patients with gallbladder cancer was 6.6 months and the MST in patients with bile duct cancer was 19 months; thus, this difference in MST was assumed to be due to a biological difference.¹⁶ In overseas clinical trials of chemotherapy for biliary tract cancer, intrahepatic cholangiocarcinoma is often included. In Japan,

however, intrahepatic cholangiocarcinoma was often excluded from clinical trials of biliary tract cancer, because this entity is classified as primary liver cancer in the “General rules for the clinical and pathological study of primary liver cancer,¹⁷” published by the Liver Cancer Study Group of Japan¹⁸ and the “TNM classification of malignant tumours,” published by the International Union Against Cancer. Also, some clinical trials include ampullary cancer and some do not. Ideally, clinical trials of chemotherapy for biliary tract cancer and the assessment of treatment results should be carried out independently according to the individual diseases, but due to the small numbers of patients with the individual diseases, making an analysis of diseases independently is difficult. Therefore, RCTs with large numbers of patients and adequate stratification of all patients concerned should be conducted to evaluate the results of chemotherapy.

The number of RCTs that have been conducted concerning chemotherapy for bile duct cancer is not so large. Outlined in Table 5 are RCTs retrieved from a literature search. In Japan, comparisons were made by Takada et al.^{3,19} between FAM and 5-FU alone and between FAM and palliative treatment, such as bypass operation. No significant difference in survival was confirmed in these RCTs, and a standard chemotherapy has not been established yet (level II).

As chemotherapy for biliary tract cancer at the present time, gemcitabine or S-1, which is covered by insurance in Japan, is recommended on the basis of the results of many phase II trials, including those performed in Japan (level III). Evidence-based standard treatment should be established in the future by conducting controlled trials with the use of these agents.

CQ 3 Does adjuvant chemotherapy after surgery have a survival benefit?

No recommendable regimen is available now, but it is hoped that adjuvant chemotherapy can be carried out as a clinical trial. (recommendation C1).

In gallbladder and bile duct cancers, early recurrence often occurs even if these patients have received curative resection; the prognosis in patients with recurrence is extremely poor. Therefore, further development of effective measures for preventing recurrence through postoperative adjuvant therapy is eagerly anticipated. In view of the low incidence of biliary tract cancer in Western countries, where a large number of clinical studies of postoperative adjuvant therapy have been conducted in other types of cancer, few RCTs of postoperative adjuvant therapy for biliary tract cancer have been carried out. On the other hand, in the East Asian region (including Japan), the incidence of biliary tract cancer is high so RCTs of postoperative adjuvant therapy have been carried out in Japan.

From 1986 to 1992, Takada et al. performed an RCT in which 508 patients with pancreas cancer and biliary tract cancer were assigned to a group in which combination chemotherapy using 5-FU and mitomycin C (MMC) was administered (MF group) and a group for whom surgery alone was conducted (control group); the results were reported with a postoperative follow-up period of 5 years.²⁰ As eligible patients, 158 patients with pancreatic cancer, 118 patients with bile duct cancer, 112 patients with gallbladder cancer, and 48 patients with ampullary cancer were chosen. Analysis was done independently in the individual diseases, and the 5-year survival rate was found to be significantly better in the MF group for gallbladder cancer (Table 6) (level II). However, according to a review of the degree of cure due to resection, a significant difference in survival rate was found only in patients with noncurative resection. On the basis of an intent-to-treat analysis, no significant difference between the MF and the control group was observed in patients with gallbladder cancer. MF therapy has not yet been established as standard postoperative adjuvant therapy in biliary tract cancer, but the efficacy

Table 6. Randomized clinical trial of adjuvant chemotherapy for pancreas and biliary tract cancer²⁰

	<i>n</i>	5-Year survival rate	<i>P</i> value
Pancreas			
Mitomycin C/5-FU	81	11.5%	NS
Surgery alone	77	18.0%	
Gallbladder			
Mitomycin C/5-FU	69	26.0%	0.037
Surgery alone	43	14.4%	
Biliary tract			
Mitomycin C/5-FU	58	26.7%	NS
Surgery alone	60	24.1%	
Ampulla of Vater			
Mitomycin C/5-FU	24	28.1%	NS
Surgery alone	24	34.3%	

of postoperative adjuvant therapy is suggested by such trials.

Todoroki summarized the results of clinical trials of chemotherapy for gallbladder cancer and verified that postoperative chemotherapy was efficacious. Most of these clinical trials were conducted using a single arm, so no regimen could be selected as a possible candidate for postoperative adjuvant therapy.²¹ Recently, chemotherapy focusing on gemcitabine for unresectable biliary tract cancer has been conducted, and regimens with good anticancer effects have sometimes been observed. However, no large RCTs of postoperative adjuvant therapy have been carried out with the use of such regimens. RCTs of postoperative adjuvant therapy, using new agents including gemcitabine and S-1, should be conducted vigorously. At the present time, no recommendable postoperative adjuvant therapy has been discovered, so clinical trials of various forms of chemotherapy are anticipated in the future.

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