

Role of chemotherapy in treatments for biliary tract cancer

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Abstract The purpose of chemotherapy in patients with advanced solid cancers, including biliary tract cancer, is generally to improve the survival and quality of life of the patients. Also, adjuvant chemotherapy is expected to increase the curability of surgery in patients scheduled to undergo surgery. Most patients with unresectable biliary tract cancer develop obstructive jaundice, and biliary drainage is needed before any of the aforementioned treatments. Once jaundice is resolved by stenting of the bile duct or bilio-intestinal bypass, cholangitis often develops, leading to rapid deterioration of the patient's general condition. Therefore, the beneficial effect of chemotherapy in such patients remains controversial. A few randomized controlled trials have demonstrated the survival benefit of chemotherapy as compared with supportive care. In one of these trials, improvement of the quality of life was also confirmed. Recently, since the survival benefit of combined gemcitabine plus cisplatin therapy over gemcitabine alone has been demonstrated in randomized controlled clinical trials, this combined regimen has been recognized as a standard therapy for unresectable biliary tract cancer. A second-line regimen is now expected to be established for patients with gemcitabine-refractory biliary tract cancer, although the significance of second-line therapy remains unclear. One of the next issues in relation to chemotherapy for biliary tract cancer is the development of molecular-targeted agents; however, few large clinical trials of such agents have been conducted for biliary tract

cancer. Various issues in chemotherapy for biliary tract cancer remain to be investigated, and global cooperation is necessary to conduct large clinical trials.

Keywords Biliary tract cancer · Chemotherapy · Survival benefit · Quality of life · Gemcitabine · Cisplatin

Introduction

Biliary tract cancer is a common cause of cancer-related death in Asia, including Japan, and Latin America. In Japan, the mortality is estimated to be 17,000 deaths annually. While surgery remains the only potentially curative treatment, the curative resection rate remains low, at approximately 40% [1]. Most patients, furthermore, develop recurrence even after curative surgery. The poor prognosis is due to the difficulty in the diagnosis of biliary tract cancer in the earlier stages and the lack of satisfactory treatments for advanced disease.

Biliary tract cancer consists of cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer; intrahepatic cholangiocarcinoma is also often included in clinical trials of treatments for biliary tract cancer. Each of these types of cancer has characteristic features and the treatment strategies and prognoses also differ. This heterogeneity has made it difficult to evaluate the efficacy of chemotherapy for biliary tract cancer, and randomized controlled trials (RCTs) with an appropriate stratification strategy, including by the tumor type, are required. Recently, a large RCT comparing combined gemcitabine plus cisplatin therapy with gemcitabine treatment alone demonstrated a survival benefit of the combined regimen over gemcitabine alone [2]. As a result, combined gemcitabine plus cisplatin therapy has come to be recognized as standard therapy for unresectable biliary tract cancer.

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The purpose of chemotherapy in patients with advanced solid cancers, including biliary tract cancer, is generally to improve their survival and quality of life (QOL), and not to achieve a cure. Also, adjuvant chemotherapy is expected to increase the curability of surgery in patients scheduled to undergo surgery. There are some difficulties in the chemotherapy of patients with biliary tract cancer. Most patients present with obstructive jaundice at diagnosis, and biliary drainage is generally needed before any of the aforementioned treatments. Once the jaundice has been resolved by stenting of the bile duct or bilio-intestinal bypass, cholangitis often develops, resulting in rapid deterioration of the patient's general condition. Thus, the beneficial effect of chemotherapy for patients with unresectable biliary tract cancer remains controversial.

In this review, based on the recent advances in chemotherapy for biliary tract cancer, the significance and roles of systemic chemotherapy for patients with unresectable biliary tract cancer are discussed.

Improvement of survival in patients with unresectable biliary tract cancer

To assess the efficacy of chemotherapy in patients with advanced biliary tract cancer, some small RCTs comparing it with supportive treatment alone have been conducted (Table 1) [3–5]. Glimelius et al. [3] reported a comparative study between chemotherapy and supportive care in 90 patients with unresectable pancreatic cancer and biliary tract cancer. In this study, 5-fluorouracil (5-FU) + leucovorin 5-FU + leucovorin + etoposide was compared with supportive care. For all the patients, the overall survival was significantly longer in the chemotherapy group than in the supportive care group (median 6.0 vs. 2.5 months, $P < 0.01$). In only the patients with biliary tract cancer, no significant difference in survival between the two groups was noted, due to the small number of patients (37 patients), and the survival in the two groups was similar (6.5 months in the chemotherapy group and 2.5 months in the supportive care group; $P = 0.1$). Takada et al. [4] conducted a comparative study in Japan comparing 5-FU + doxorubicin + mitomycin C (FAM) with palliative treatment, such as bypass, in patients with unresectable pancreatic cancer, gallbladder cancer, and bile duct cancer. No improvement in the prognosis was demonstrated in either treatment group overall, but longer survival was achieved in the chemotherapy group than in the control group for the 18 patients with gallbladder cancer (median 5.16 months in the chemotherapy arm and 2.4 months in the control arm).

Recently, a comparative study of modified gemcitabine/oxaliplatin (Gemox), 5-FU/folinic acid (FA), and best supportive care was reported in patients with unresectable

gallbladder cancer [5]. The modified Gemox regimen yielded a statistically significantly higher response rate, progression-free survival, and overall survival as compared with 5-FU/FA chemotherapy and best supportive care. Although these studies included only a small number of patients, these results suggest a survival benefit of chemotherapy in patients with unresectable biliary tract cancer and adequate organ and bone marrow function, as long as obstructive jaundice and cholangitis can be controlled.

Promising agents for biliary tract cancer were examined in retrospective studies before a large RCT was conducted. In a pooled analysis of 104 phase II studies, significant correlations of the response rate and tumor control rate with the survival times were observed, and the response rate and tumor control rate were highest in the patients treated with a gemcitabine–platinum combination [6]. Four hundred thirteen consecutive patients administered non-surgical treatments were reviewed in a Japanese retrospective study [7]. To clarify the impact of systemic chemotherapy on the survival and identify promising agents for biliary tract cancer, the hazard ratios and 95% confidence intervals (CI) were estimated by Cox regression by subgroup of chemotherapeutic regimen as compared with best supportive care. The median overall survival in the best supportive care group was 3.12 months and that in the chemotherapy group was 7.38 months, and a statistically significant difference in survival was noted between the two groups ($P = 0.0001$). The adjusted hazard ratio in the Cox regression model using confounders for gemcitabine was 0.53 (95% CI 0.34–0.82) and for cisplatin-based regimens it was 0.49 (95% CI 0.36–0.99). Thus, gemcitabine and platinum were identified as promising agents for the treatment of biliary tract cancer.

A randomized phase II study (ABC-01) comparing gemcitabine alone with gemcitabine plus cisplatin was conducted in the United Kingdom [8]. It demonstrated superior 6-month progression-free survival (57.1 vs. 45.5%) with acceptable toxicity in the gemcitabine 1,000 mg/m² plus cisplatin 25 mg/m² group as compared with that in the gemcitabine 1,000 mg/m²-alone group, and was therefore expanded to a phase III study (ABC-02). The results revealed a statistically significant improvement in the overall survival in the gemcitabine-plus cisplatin group as compared with that in the gemcitabine-alone group (Table 2) [2]. The BT-22 study was planned in Japan following the promising results of the ABC-01 study, and results similar to those of the ABC-02 study were demonstrated in Japanese patients with biliary tract cancer (Table 2) [9].

Improvement of the quality of life

It is difficult to assess efficacy based on the QOL, especially in patients with biliary tract cancer, because there are

Table 1 Trials comparing chemotherapy and supportive care in patients with unresectable biliary tract cancer

	<i>n</i>	Median OS (months)	<i>P</i> value	References
5-FU/leucovorin or 5-FU/leucovorin/etoposide	47	6	<0.01	Glimelius et al. [3]
Supportive care	43	2.5		
5-FU/doxorubicin/mitomycin C	42	4.96	0.283	Takada et al. [4]
Control	41	4.7		
Gemcitabine/oxaliplatin	27	9.5	0.039	Sharma et al. [5]
5-FU/folinic acid	28	4.6		
Best supportive care	27	4.5		

5-FU fluorouracil, OS overall survival

Table 2 Efficacy of first-line chemotherapy for unresectable biliary tract cancer

Regimen	<i>n</i>	Response rate (%)	Median PFS (months)	Median OS (months)	References
Gemcitabine	206	15.5	5.0	8.3	Valle et al. [2]
Gemcitabine/cisplatin	204	26.1	8.0	11.7	Okusaka et al. [9]
Gemcitabine	42	11.9	3.7	7.7	
Gemcitabine/cisplatin	41	19.5	5.8	11.2	Cho et al. [13]
Gemcitabine/capecitabine	45	32	6.0	14.0	
Gemcitabine/capecitabine	75	29	6.2	12.7	Riechelmann et al. [14]
Gemcitabine/capecitabine	44	25	7.2	13.2	Koeberle et al. [15]
Gemcitabine/S-1	35	34.3	5.9	11.6	Sasaki et al. [16]

PFS progression-free survival, OS overall survival

many specific symptoms due to tumor progression and/or obstruction of the bile duct in patients with advanced biliary tract cancer. In the ABC-02 study, it was demonstrated that patients who received gemcitabine had a significantly increased incidence of grade 3 or 4 liver function test abnormalities, possibly as a result of inferior disease control and biliary drainage as compared with that in the group administered combined gemcitabine plus cisplatin therapy [2]. This finding suggests that a higher efficacy of chemotherapy against tumor progression in patients with biliary tract cancer might contribute to maintaining the patency of the bile duct and prevent cholangitis due to re-obstruction of the bile duct.

Improvement in the QOL was also examined in a trial comparing chemotherapy and supportive care, with QOL assessed by using the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) version 1.0 questionnaire [3]. The results revealed a significant QOL improvement in the chemotherapy group ($P < 0.01$); a 36% improvement was observed in the chemotherapy group (pancreatic cancer 38%, biliary tract cancer 33%) and a 10% (pancreatic cancer 13%, biliary tract cancer 5%) improvement was shown in the supportive care group. In the analysis by symptom, significant improvements of pain, fatigue, appetite, and dyspnea after 2 months, and that of pain and dyspnea after 4 months were observed in the chemotherapy group.

Second-line therapy for unresectable biliary tract cancer

Now that first-line chemotherapy has been established, the development of a second-line therapy would be the next logical step to improve survival in patients with unresectable biliary tract cancer. New oral fluoropyrimidines, such as capecitabine and tegafur/gimeracil/oteracil potassium (S-1), which are prodrugs of FU, have been investigated as monotherapy or in combination with gemcitabine. There are few prospective clinical trials that have focused on second-line therapy only in patients with biliary tract cancer. S-1 was investigated in patients with gemcitabine-refractory biliary tract cancer in a phase II study [10]. There were 3 confirmed partial responses (7.5%) among the 40 patients assessed, and 22 patients (55%) with stable disease. The median progression-free and overall survivals were 2.5 and 7.5 months, respectively. Despite the acceptable toxicity of S-1, its efficacy was modest, and these results could serve as reference data for the development of second-line therapy.

The impact of second-line therapy after gemcitabine-based chemotherapy was assessed in the ABC-02 and BT-22 studies [11]. In the ABC-02 trial conducted in the United Kingdom, the treatment of patients with disease progression was left to individual clinicians' discretion, and was best supportive care for the majority, with only

17% of patients receiving further chemotherapy, mostly 5-FU-based chemotherapy. On the other hand, in the BT-22 study conducted in Japan, 73% of the patients in the gemcitabine-plus-cisplatin group and 78% of the patients in the gemcitabine-alone group received post-study chemotherapy. S-1 was approved for the treatment of biliary tract cancer based on the results of a first-line phase II study in Japan [12], and, consequently, more than 60% of the patients in the BT-22 study were treated with S-1 as second-line therapy [9]. This difference in the rate of application of second-line therapy could have potentially improved the overall survival in the BT-22 study as compared with that in the ABC-02 study, although the overall survival in the two studies was quite similar. So far, therefore, the impact of second-line therapy in patients with gemcitabine-refractory biliary tract cancer remains unclear.

Future perspectives on chemotherapy for unresectable biliary tract cancer

Gemcitabine has been recognized as a key drug for the treatment of biliary tract cancer, and many phase II studies of gemcitabine have been conducted. The combination of gemcitabine plus the oral fluoropyrimidines capecitabine or S-1 also showed promising activity in phase II studies. These phase II studies yielded response rates of 25–34% and a median overall survival of 11.6–14.0 months (Table 2) [13–16]. A randomized phase II study comparing combined gemcitabine plus S-1 chemotherapy and S-1 monotherapy was conducted by the Japanese Clinical Oncology Group (JCOG) to evaluate the efficacy and safety of the two regimens and to determine which was the more promising regimen as a test arm regimen for comparison with the current standard regimen; namely, gemcitabine plus cisplatin [17]. If the combination of gemcitabine plus S-1 is found to be promising, a large RCT comparing this combination with gemcitabine plus cisplatin would be warranted.

One of the next issues that need to be addressed is whether molecular-targeted agents might also exert activity against biliary tract cancer. To date, no large clinical trials of molecular-targeted agents have been conducted for biliary tract cancer; however, some of these agents appear to offer promise. A combination of Gemox plus bevacizumab, a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), yielded promising results in a phase II study, with a response rate of 40% and median overall survival of 12.7 months [18]. A phase II study of Gemox plus cetuximab, an anti-epidermal growth factor receptor (EGFR) antibody, also demonstrated promising efficacy, with a response rate of 63% and

median overall survival of 15.2 months [19]. A randomized phase II study comparing Gemox plus cetuximab and Gemox alone has been conducted in France [20], and has been expanded to a phase III study.

Usage of monotherapy with targeted agents as second-line chemotherapy is also expected. Some preclinical experiences show that VEGF receptor or EGFR inhibitors administered alone may exert efficacy against biliary tract cancer. In many patients with progressive disease receiving first-line chemotherapy with the relatively toxic regimen of gemcitabine plus cisplatin or Gemox, the general condition may be poor, and serious cholangitis can easily develop. Less toxic therapy, such as monotherapy with a targeted agent, may be useful in such patients.

Conclusions

Effective chemotherapy is necessary to improve the survival and QOL of patients with biliary tract cancer. Because biliary tract cancer is a relatively rare disease as compared with other gastrointestinal cancers, such as colorectal cancer or gastric cancer, large clinical trials of treatments for this cancer are difficult to conduct. Efforts to establish new standard chemotherapies are ongoing, and international collaboration is necessary for the success of these efforts.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Nagakawa T, Kayahara M, Ikeda S, Futakawa S, Kakita A, Kawarada H, et al. Biliary tract cancer treatment: results from the Biliary Tract Cancer Statistics Registry in Japan. *J Hepatobiliary Pancreat Surg.* 2002;9:569–75.
2. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.* 2010;362:1273–81.
3. Glimelius B, Hoffman K, Sjöden PO, Jacobsson G, Sellström H, Enander LK, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol.* 1996;7:593–600.
4. Takada T, Nimura Y, Katoh H, Nagakawa T, Nakayama T, Matsushiro T, et al. Prospective randomized trial of 5-fluorouracil, doxorubicin, and mitomycin C for non-resectable pancreatic and biliary carcinoma: multicenter randomized trial. *Hepatogastroenterology.* 1998;45:2020–6.
5. Sharma A, Dwary AD, Mohanti BK, Deo SV, Pal S, Sreenivas V, et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. *J Clin Oncol.* 2010;28:4581–6.
6. Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. *Br J Cancer.* 2007;96:896–902.
7. Yonemoto N, Furuse J, Okusaka T, Yamao K, Funakoshi A, Ohkawa S, et al. A multi-center retrospective analysis of survival

- benefits of chemotherapy for unresectable biliary tract cancer. *Jpn J Clin Oncol*. 2007;37:843–51.
8. Valle JW, Wasan H, Johnson P, Jones E, Dixon L, Swindell R, et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study—the UK ABC-01 Study. *Br J Cancer*. 2009;101:621–7.
 9. Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer*. 2010;103:469–74.
 10. Suzuki E, Ikeda M, Okusaka T, Nakamori S, Ohkawa S, Nagakawa T, et al. A multicenter phase II of S-1 in gemcitabine-refractory biliary tract cancer. *J Clin Oncol*. 2010;28:15s (suppl; abstr 4145).
 11. Furuse J, Okusaka T, Bridgewater J, Taketsuna M, Wasan H, Koshiji M, et al. Lessons from the comparison of two randomized clinical trials using gemcitabine and cisplatin for advanced biliary tract cancer. *Crit Rev Oncol Hematol*. 2011; 80:31–39.
 12. Furuse J, Okusaka T, Boku N, Ohkawa S, Sawaki A, Masumoto T, et al. S-1 monotherapy as first-line treatment in patients with advanced biliary tract cancer: a multicenter phase II study. *Cancer Chemother Pharmacol*. 2008;62:849–55.
 13. 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.
 14. Riechelmann RP, Townsley CA, Chin SN, Pond GR, Knox JJ. Expanded phase II trial of gemcitabine and capecitabine for advanced biliary cancer. *Cancer*. 2007;110:1307–12.
 15. Koeberle D, Saletti P, Borner M, Gerber D, Dietrich D, Caspar CB, et al. Patient-reported outcomes of patients with advanced biliary tract cancers receiving gemcitabine plus capecitabine: a multicenter, phase II trial of the Swiss Group for Clinical Cancer Research. *J Clin Oncol*. 2008;26:3702–8.
 16. Sasaki T, Isayama H, Nakai Y, Ito Y, Kogure H, Togawa O, et al. Multicenter, phase II study of gemcitabine and S-1 combination chemotherapy in patients with advanced biliary tract cancer. *Cancer Chemother Pharmacol*. 2010;65:1101–7.
 17. Takashima A, Morizane C, Ishii H, Nakamura K, Fukuda H, Okusaka T, et al. Randomized phase II study of gemcitabine plus S-1 combination therapy vs. S-1 in advanced biliary tract cancer: Japan Clinical Oncology Group Study (JCOG0805). *Jpn J Clin Oncol*. 2010;40:1189–91.
 18. Zhu AX, Meyerhardt JA, Blaszkowsky LS, Kambadakone AR, Muzikansky A, Zheng H, et al. Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose PET with clinical outcome: a phase 2 study. *Lancet Oncol*. 2010;11: 48–54.
 19. Gruenberger B, Schueller J, Heubrandtner U, Wrba F, Tamandl D, Kaczirek K, et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. *Lancet Oncol*. 2010;11:1142–8.
 20. Malka D, Trarbach T, Fartoux L, Mendiboure J, de la Fouchardière C, Viret F, et al. A multicenter, randomized phase II trial of gemcitabine and oxaliplatin (GEMOX) alone or in combination with biweekly cetuximab in the first-line treatment of advanced biliary cancer: interim analysis of the BINGO trial. *J Clin Oncol*. 2009;27 suppl:206s (abstr 4520).