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Chemotherapy of Cholangiocarcinoma: Current Management and Future Directions

Jung Hyun Jo and Si Young Song

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Abstract

Cholangiocarcinoma is a relatively rare form of gastroenterological cancer that divided into intrahepatic, perihilar, and distal bile duct cancer. Approximately, 10,000 new cases are diagnosed annually in the United States, and a 5-year survival rate is below 20%. While only surgical resection can provide a cure, most of cholangiocarcinomas are detected at inoperable stage and associated with poor prognosis. Moreover, cholangiocarcinoma has a high recurrence rate, even after curative surgery. Therefore, chemotherapy has an important role in the treatment of patients with cholangiocarcinoma. International efforts by physicians and researchers are revealing genetic factors of cholangiocarcinoma progression, which will identify early diagnostic markers and novel therapeutic targets. In this chapter, current strategies of adjuvant, neoadjuvant, and palliative chemotherapy will be discussed, as well as expectant future therapeutic targets and development of individualized therapies.

Keywords: cholangiocarcinoma, biliary tract cancer, biliary tract neoplasms, chemotherapy, precision medicine

1. Introduction

Cholangiocarcinoma is a rare malignant tumor that originates from the epithelial cells of the bile duct system. About 90% of cholangiocarcinoma are adenocarcinoma and divided into three forms based on histologic growth pattern as mass-forming, periductal-infiltrating, and intraductal-growing [1]. Generally, cholangiocarcinoma can be divided by anatomical location of biliary tree, as intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma including perihilar cholangiocarcinoma and distal bile duct cancer. Extrahepatic

cholangiocarcinoma is a more common form of cholangiocarcinoma, comprising approximately 80–90% of cholangiocarcinoma. Extrahepatic cholangiocarcinoma consists of perihilar cholangiocarcinoma and distal bile duct cancer. Perihilar cholangiocarcinoma, also called Klatskin tumor, is the most common type, accounting for approximately 50–60% of all cases, and can be defined as a tumor located above the junction of the cystic duct up to and including the second-order biliary branches of the right and left bile ducts [2]. Distal cholangiocarcinoma arose from distal biliary tract above the ampulla of Vater, accounting or approximately 20–30% of all cholangiocarcinoma. Intrahepatic cholangiocarcinoma is in liver parenchyma, accounting for 10–20% of cholangiocarcinoma.

Approximately 10,000 new cases are diagnosed annually in the United States, and 5-year survival rate is below 20% [3]. In Korea, there are 11.2 new cases per 100,000 people annually, and a 5-year survival rate is 29.2% according to cancer statics in 2014 [4]. While only surgical resection can provide a cure, most of cholangiocarcinomas are detected at inoperable stage and associated with poor prognosis. Moreover, cholangiocarcinoma has high recurrence rate, even after curative surgery [5]. Therefore, chemotherapy has an important role in the treatment of patients with cholangiocarcinoma. However, there are only few therapeutic options that establish an effective chemotherapy for advanced cholangiocarcinoma. International efforts by physicians and researchers are revealing genetic factors of cholangiocarcinoma progression, which will identify early diagnostic markers and novel therapeutic targets.

In this chapter, current strategies of adjuvant, neoadjuvant, and palliative chemotherapy will be discussed as well as expectant future therapeutic targets and development of individualized therapies.

2. Adjuvant chemotherapy

2.1. Necessity of adjuvant chemotherapy

Necessity of adjuvant chemotherapy for cholangiocarcinoma is based on prognosis after surgical treatments. Surgery is only curative therapy of cholangiocarcinoma; however, a 2-year survival of cholangiocarcinoma after curative aim surgery was reported very poor. According to a prospective study of 225 patients with hilar cholangiocarcinoma, 80 patients underwent resection, and 48.8% died of disease by 28 months [6]. In this situation, selection of high-risk patients for recurrence after surgery became important. Due to anatomical heterogeneity of cholangiocarcinoma and proximity to other organs, many of previous studies were including cancers originated from the gallbladder or ampulla of Vater as well as intrahepatic and extrahepatic cholangiocarcinoma. Long-term outcomes of curative surgery of cholangiocarcinoma are various according to postoperative stage including nodal status, anatomical location, and histologic margin status. Despite of native difficulties of research about cholangiocarcinoma, the most important conditions proven by previous studies are nodal involvements and histologic margin status after surgery.

A couple of retrospective studies reported postoperative nodal status that is a significant prognostic factor after surgery of extrahepatic cholangiocarcinoma. About 104 patients with distal

bile duct tumors were identified by prospective database. By univariate and multivariate analysis, resectability and negative node status ($P < 0.001$) were the only predictors of favorable outcome [7]. A retrospective single-center experience details of 151 patients after surgical resection of central bile duct carcinoma reported only lymph node metastases, and residual tumor stage proved to be of independent prognostic significance in a multivariate Cox analysis [8]. Another retrospective study of 46 patients who had resection of hilar cholangiocarcinoma by major hepatectomy, bile duct resection, and regional lymphadenectomy reported R0 resection and lymph node metastasis were associated with survival [9]. According to a retrospective study of 320 patients with perihilar cholangiocarcinoma who underwent resection, upon multivariate analysis of the 146 patients with lymph node metastasis, the number of involved nodes (single versus multiple) was identified as an independent prognostic factor (RR of 1.61, $P = 0.045$) [10].

There were studies reported that nodal status was also important in intrahepatic cholangiocarcinoma. About 93 patients who underwent laparotomy for ICC were identified retrospectively, and 46 who underwent curative resection and systematic lymphadenectomy. An increased ratio of positive to total harvested lymph nodes was prognostic for adverse outcome in lymph node-positive patients [11]. In a total of 60 liver resections for mass-forming-type intrahepatic cholangiocarcinoma, the lymphatic invasion index and histological grade were statistically independent prognostic factors for overall survival and recurrence-free survival in multivariate analysis [12].

Resection margin status was also reported as strong independent prognostic factor after surgery in cholangiocarcinoma. In a retrospective analysis of 84 patients with extrahepatic cholangiocarcinoma who underwent surgical resection, ductal resection margin status was classified as negative (n = 64 patients), positive with carcinoma in situ (n = 11 patients), or positive with invasive carcinoma (n = 9 patients). The ductal margin status was found to be a strong independent prognostic factor by both univariate ($P = 0.0002$) and multivariate ($P = 0.0039$) analyses [13]. In 109 patients with resected perihilar tumors, the 1-, 3-, and 5-year survival was 68, 30 and 11%, respectively. The median survival was 19 months. The addition of hepatic lobectomy did not alter the survival rate. Negative margins and negative lymph node status were associated with improved survival [14]. In a prospective study of 225 patients with hilar cholangiocarcinoma, 80 patients underwent resection, and 62 patients showed R0 resection. In the 219 patients whose disease could be staged, the proposed system predicted resectability and the likelihood of an R0 resection and correlated with metastatic disease and survival [6]. In a prospective study of 27 patients with cholangiocarcinoma at the confluence of the hepatic ducts who underwent resection, the difference in survival times between patients with histologic clearance and those with microscopically positive or close (less than 1 mm) resection margins was significant statistically ($P = 0.037$) [15].

In addition, lymphovascular and perineural invasion and large tumor size have been reported as independent predictors of recurrence and reduced overall survival after surgical resection of intrahepatic cholangiocarcinoma [16, 17]. It might be confusing to analyze the studies of bile duct cancers that originate in various locations. However, plenty of studies above reported that marginal resection and lymph node involvement status are significantly associated with surgical outcomes and patient survival. To improve survival of patients after surgical resection, studies of adjuvant chemotherapy were performed.

2.2. Indication and efficacy of adjuvant chemotherapy

Cholangiocarcinoma has various subtypes according to anatomical location, and most of the studies about adjuvant chemotherapy contain patients with gallbladder cancer, ampulla of Vater cancer, or pancreatic cancer. In addition to heterogeneity of the origin of cancers, regimen of chemotherapies and disease status such as post-op stage including lymph node involvement or margin status are also various. Majority of previous studies were retrospective design, except one phase III trial that had not shown a significant outcome improvement after adjuvant chemotherapy.

Several studies were performed to evaluated efficacy of adjuvant chemotherapy for cholangiocarcinoma, and the results were controversial. A retrospective study reported that the benefit of adjuvant chemotherapy after surgery in cholangiocarcinoma is questionable. According to the study including gallbladder cancer and cholangiocarcinoma, of the 157 patients, 17.8% received neoadjuvant chemotherapy, and 48.7% received adjuvant chemotherapy, while 15.8% received adjuvant chemoradiotherapy. Patients with negative margins of at least 1 cm had a 5-year survival rate of 52.4% ($P < 0.01$). Adjuvant therapy did not significantly prolong survival in 94 patients with cholangiocarcinoma [18]. There were other studies that provide positive evidence of adjuvant chemotherapy of cholangiocarcinoma. A retrospective review of 115 patients with hilar cholangiocarcinoma and patients treated with chemotherapy postoperatively had a survival of 43.15 ± 21.02 months, which was significantly longer than the survival of patients who received no postoperatively chemotherapy (36.97 ± 15.99 months; $P < 0.05$) [19].

A systematic review and meta-analysis about adjuvant chemotherapy of cholangiocarcinoma and gallbladder cancer supported adjuvant chemotherapy for biliary tract cancer. About 20 studies involving 6712 patients were analyzed in the study. Among the 20 studies, there were 1 randomized trial of chemotherapy alone, 2 registry analyses, and 17 institutional series. In the overall population, pooled data showed a nonsignificant improvement in survival with any adjuvant therapy compared with surgery alone (OR, 0.74; $P = 0.06$, and for bile duct cancers OR, 0.71; $P = 0.10$). However, after the two registry analyses were excluded, receiving chemotherapy demonstrated statistically greater benefit than surgery alone ($P = 0.02$). In subgroup analysis, the greatest benefit for adjuvant therapy was in those with lymph node-positive disease (OR, 0.49; $P = 0.004$) and R1 disease (OR, 0.36; $P = 0.002$) [20].

About the chemotherapy regimen, there is only one phase III randomized controlled studies that had proven limited survival benefit. A phase III randomized trial of adjuvant chemotherapy of cholangiocarcinoma, the European Study Group for Pancreatic Cancer (ESPAC)-3 periampullary trial, was performed in 100 centers in Europe, Australia, Japan, and Canada. Of the 428 patients included in the primary analysis, 297 had ampullary, 96 had bile duct, and 35 had other cancers. About 144 patients were assigned to the observation group, 143 patients received fluorouracil chemotherapy, and the other 141 patients received gemcitabine chemotherapy. Median survival for the observation group was 35.2 months, for patients treated with fluorouracil plus folinic acid 38.9 months, and for patients treated with gemcitabine 45.7 months. The hazard ratio (HR) for fluorouracil plus folinic acid versus observation was 0.95 ($P = 0.74$), and for gemcitabine versus observation, 0.77 ($P = 0.10$), not significant by log-rank analysis across the three groups ($P = 0.23$). In secondary analyses adjusting for prognostic variables

using multiple regression analysis, the HR for chemotherapy compared with observation was 0.75 (P = 0.03) and for gemcitabine 0.70 (P = 0.03). Conclusively, adjuvant chemotherapy was not associated with a significant survival benefit in the primary analysis compared with observation; however, multivariate analysis adjusting compounding factors showed survival benefits associated with adjuvant chemotherapy, especially with gemcitabine [21].

According to the results of the meta-analysis and ESPAC-3 trail, adjuvant chemotherapy is effective in patients with cholangiocarcinoma after curative surgery, especially with lymph node-positive and resection margin-positive disease.

2.3. Guideline recommendation for adjuvant chemotherapy

There were two guidelines about adjuvant chemotherapy of cholangiocarcinoma by expert groups.

The National Comprehensive Cancer Network (NCCN) suggests adjuvant chemotherapy after curative surgery of cholangiocarcinoma and regimens according to lymph node and margin status [22]. Although there are limited clinical trial data to establish a standard chemotherapy regimen for intrahepatic cholangiocarcinoma after surgery, recommended regimens based on fluoropyrimidine or gemcitabine chemotherapy. In patients with no residual local disease (R0) resection, observation or clinical trial can be a choice with fluoro-pyrimidine-based or gemcitabine-based chemotherapy. If the patients have a disease with microscopic margin positive (R1) or positive regional lymph nodes, chemotherapy is rec-ommended than observation. In addition to fluoropyrimidine-based or gemcitabine-based chemotherapy, clinical trial or fluoropyrimidine chemoradiation can be a treatment option. In spite of receiving curative surgery, patients may have residual local disease. In this situ-ation, clinical trial, locoregional therapy such as transarterial chemoembolization, or best supportive care is included as options with chemotherapy with gemcitabine or fluoropy-rimidine. NCCN guideline for adjuvant chemotherapy of extrahepatic cholangiocarcinoma is also based on fluoropyrimidine-based or gemcitabine-based chemotherapy. However, there are limited clinical trial data to set a standard therapy. If available, enrollment in a clinical trial is encouraged. If the disease had negative margin or carcinoma in situ at margin without regional nodes, observation, fluoropyrimidine chemoradiation, fluoropy-rimidine−/gemcitabine-based chemotherapy, or clinical trial is recommended as treatment options. If patients had positive margin (R1 or R2) or positive regional nodes, fluoropy-rimidine chemoradiation followed by additional fluoropyrimidine-based or gemcitabine-based chemotherapy can be considered, as well as fluoropyrimidine−/gemcitabine-based chemotherapy or clinical trial.

The European Society of Medical Oncology (ESMO) clinical practice guidelines for biliary cancer suggest adjuvant chemotherapy for intrahepatic and extrahepatic cholangiocarcinoma after curative aim surgery [23]. ESMO recommendations offer adjuvant therapy to patients on the understanding that the evidence base is weak and encourage enrollment in clinical trials. When the results from previous meta-analysis were employed, chemoradiation is rec-ommended with 45 Gy dose of radiotherapy in fractions of 1.8 or 2 Gy with concurrent 5-fluo-rouracil or capecitabine [IV, C].

3. Neoadjuvant chemotherapy

There are not enough evidences about neoadjuvant chemotherapy of cholangiocarcinoma. In a retrospective study including gallbladder cancer and cholangiocarcinoma, neoadjuvant therapy delayed surgical resection on average for 6.8 months ($p < 0.0001$). Immediate resection increased median survival from 42.3 to 53.5 months ($p = 0.01$) [18]. A couple of reports addressed possibility to use neoadjuvant chemoradiation before liver transplantation in patients with cholangiocarcinoma [24–28]. In a study of 287 patients with perihilar cholangiocarcinoma using neoadjuvant therapy, 71 patients dropped out before liver transplantation (rate, 11.5% in 3 months). Intent-to-treat survival rates were 68 and 53%, 2 and 5 years after therapy, respectively; posttransplant recurrence-free survival rates were 78 and 65%, respectively [25]. In a retrospective study of patients with hilar cholangiocarcinoma, 71 patients entered in the protocol combining neoadjuvant radiotherapy, chemosensitization, and orthotopic liver transplantation. About 38 patients underwent liver transplantation, and 26 (48%) underwent resection One-, 3-, and 5-year patient survivals were 92, 82, and 82% after transplantation and 82, 48, and 21% after resection ($P = 0.022$) [27]. Of the 57 patients with intrahepatic and hilar cholangiocarcinoma, neoadjuvant and adjuvant therapies resulted in better patient survival after liver transplantation compared with no therapy or adjuvant therapy only (47% versus 20% versus 33%, respectively; $P = 0.03$) [28]. Despite the lack of result from randomized controlled trial, neoadjuvant chemoradiation might be one of treatment options in selected patients with hilar cholangiocarcinoma before liver transplantation. Further prospective trials are needed in large population for establish neoadjuvant therapy as a reliable therapeutic option in cholangiocarcinoma.

4. Palliative chemotherapy

Palliative chemotherapy has an important role in the treatment of advanced and recurrent cholangiocarcinoma. The current standard therapy for patients with inoperable cholangiocarcinoma is a combination of gemcitabine and cisplatin chemotherapy. A previous randomized controlled trial revealed that combining gemcitabine with cisplatin improved the overall survival by 3.6 months compared to gemcitabine alone [29]. According to the study, gemcitabine with cisplatin combination became the standard therapy of advanced and metastatic cholangiocarcinoma. However, there is no established second-line palliative chemotherapy that could be used after failure of gemcitabine-based chemotherapy. Moreover, cisplatin is associated with severe toxicity, including dose-dependent nephrotoxicity and neurotoxicity, which may limit the opportunities for second-line treatment after disease progression.

4.1. First-line chemotherapy

Benefits of chemotherapy for advanced biliary tract cancer were reported by various studies. In a phase III trial of patients with 53 pancreatic cancer and 37 biliary tract cancer, patients were randomized to a chemotherapy group in addition to the best supportive care or to the

best supportive care group. Chemotherapy was either sequential 5-fluorouracil/leucovorin combined with etoposide or in elderly and poor performance patients, the same regimen without etoposide. Overall survival was significantly longer in the chemotherapy group (median 6 versus 2.5 months, $P < 0.01$) [30]. A pooled analysis of clinical trials reported analysis of the effect of chemotherapy in advanced biliary tract cancer. The study included 104 trials with 2810 patients, thereof 634 responders and 1368 patients with tumor control. Superior response rates and tumor control rates of gemcitabine and platinum-containing regimens were found in the results [31]. A multicenter retrospective study showed that patients receiving gemcitabine had a benefit in survival compared to cisplatin-based regimen or fluoropyrimidine-based regimen or the best supportive care in 304 patients with advanced biliary tract cancer [32]. Upon a base of the results of the previous studies about the efficacy of the first-line chemotherapy for advanced cholangiocarcinoma, a lot of phase II studies were tried to evaluate therapeutic efficacy of combination chemotherapy in advanced cholangiocarcinoma.

4.1.1. Fluoropyrimidine-based combination therapies

Several studies evaluated fluoropyrimidine-based combination therapies. A randomized phase II trial of weekly high-dose 5-fluorouracil with and without folinic acid and cisplatin in patients with 58 advanced biliary tract carcinoma reported similar response rate, progression-free survival, and overall survival [33]. Another phase II trial in 42 patients with advanced biliary tract carcinoma reported 5-fluorourasil continuous infusion, and low-dose consecutive cisplatin therapy appeared to be a useful modality with over all response rates (42.9%) and median survival time (225 days) [34].

4.1.2. Gemcitabine-based combination therapies

A couple of gemcitabine-based combination therapies were tried in advanced cholangiocarcinoma. One randomized phase II trial compared mitomycin C in combination with capecitabine or biweekly high-dose gemcitabine in patients with 51 advanced biliary tract cancer. As a result, mitomycin C in combination with capecitabine seems to be superior in terms of response rate (31 versus 20%), progression-free survival (5.3 versus 4.2 months), and overall survival (9.25 versus 6.7 months) [35]. Gemcitabine with oxaliplatin combination therapy was tried in phase II trials [36–38]. These studies demonstrated moderate efficacy and tolerability. In one of the studies of 70 patients with advanced biliary tract cancer, the objective response rate was 20.5% in non-bladder biliary tract cancers [37]. Combination of capecitabine with gemcitabine therapy demonstrated active and well-tolerated performance as first-line chemotherapy for advanced biliary cancer [39–41]. In a phase II trial, a total of 44 patients received a combination of capecitabine with gemcitabine as first-line therapy and reported median time to disease progression of 6 months and overall survival of 14.0 months [39]. In another phase II trial, capecitabine plus cisplatin combination was reported as well-tolerated regimen for advanced biliary cancer [42]. Some of the study groups reported trials of gemcitabine- and 5-fluorouracil-based combination therapy [43, 44]. With 42 advanced biliary tract cancer patients, a combination of gemcitabine, 5-fluorouracil (5-FU), and leucovorin (LV) demonstrated median time to disease progression as 4.6 months and median survival period as 9.7 months [43].

Triplet chemoregimen also has been tried as first-line chemotherapy for advanced diseases [44–46]. A phase III study of 5-FU, etoposide, and leucovorin (FELV) compared to epirubicin, cisplatin, and 5FU (ECF) was tried in patients with advanced biliary tract cancer. The median overall survival for ECF was 9.02 months and FELV 12.03 months ($p = 0.2059$) in 54 patients randomly assigned to each arm. Objective response rates were similar for both arms (ECF 19.2% versus FELV 15%, $p = 0.72$). However, grade 3/4 neutropenia was significantly increased with FELV versus ECF (53.8 versus 29.5%, $P = 0.020$). In conclusion, ECF did not improve OS compared to FELV, but was associated with less acute toxicity [45].

4.1.3. Gemcitabine with cisplatin combination therapy

Among gemcitabine-based chemotherapy combination, there were several studies of gemcitabine plus cisplatin combination. These studies evaluated efficacy and safety of gemcitabine plus cisplatin combination with one-armed phase II trial, and they reported potent efficacy and good tolerability of this combination [47–49]. A randomized phase II trial, the advanced biliary cancer (ABC)-01 trial, had found gemcitabine with cisplatin combination associated with an improved tumor control rate, 6 months of progression-free survival (47.7–57.1%) compared to gemcitabine alone in 86 patients with advanced cholangiocarcinoma [50]. ABC-01 trial was extended to a phase III trial, the ABC-02 trail, and the study results were published in 2010. A total of 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer were randomly assigned to either cisplatin followed by gemcitabine or gemcitabine alone. The median overall survival was 11.7 months in the cisplatin-gemcitabine group and 8.1 months among the gemcitabine group ($P < 0.001$). The median progression survival (8.0 versus 5.0 months, $P < 0.001$) and tumor control rate (81.4 versus 71.8%, $p = 0.049$) were improved in cisplatin-gemcitabine group. Adverse events were similar in the two groups, with the exception of more neutropenia in the cisplatin-gemcitabine group [29]. After ABC-02 trial, another study of 84 patients with advanced cholangiocarcinoma also reported that cisplatin-gemcitabine combination showed better survival rate and survival time compared to gemcitabine alone [51].

According to the results of ABC-02 trial, gemcitabine plus cisplatin combination became the standard treatment option for first-line chemotherapy for advanced and metastatic cholangiocarcinoma.

4.1.4. Target agents

In addition to combination of cytotoxic chemotherapy agents, combination regimen with target agents was studied in several phase II trials.

A couple of studies evaluated a possibility of epidermal growth factor receptor (EGFR) inhibitors as combination agent with conventional chemotherapeutic agents. A phase II trial of gemcitabine, irinotecan, and panitumumab in advanced cholangiocarcinoma demonstrated the median progression-free survival as 9.7 months and the median overall survival as 12.9 months in 35 patients [52]. Another EGFR-targeted monoclonal antibody, cetuximab, was tried in phase II studies. In 30 patients with advanced biliary tract cancer, cetuximab,

gemcitabine, and oxaliplatin combination demonstrated 63% of objective response rate (10% of complete response and 53% of partial response) [53]. Because of the promising results of this study, the addition of cetuximab to gemcitabine and oxaliplatin did not seem to enhance the activity of chemotherapy in patients with advanced biliary cancer in the randomized phase II BINGO study. In the study, 76 patients were assigned to chemotherapy plus cetuximab and 74 to chemotherapy alone. The median progression-free survival was 6.1 versus 5.5 months, and the medial overall survival was 11.0 versus 12.4 months in chemotherapy plus cetuximab and chemotherapy alone group, respectively [54].

Another phase II study tried the application of sorafenib, an oral multi-tyrosine kinase inhibitor, with gemcitabine. Gemcitabine plus sorafenib versus gemcitabine alone was compared in advanced biliary tract cancer, and there was no difference in the median progression-free survival for gemcitabine plus sorafenib versus gemcitabine alone (3.0 versus 4.9 months, $P = 0.859$) and no difference for median overall survival (8.4 versus 11.2 months, $P = 0.775$). In conclusion, the addition of sorafenib to gemcitabine did not demonstrate improved efficacy in advanced biliary tract cancer patients [55].

Cediranib, an oral inhibitor of VEGF receptors 1, 2, and 3, was evaluated in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer by a randomized phase II trial. As a result, cediranib did not improve the progression-free survival of patients with advanced biliary tract cancer in combination with cisplatin and gemcitabine compared to placebo (8.0 versus 7.4 months, $p = 0.72$) [56].

With the results described above, there was not enough evidence to use target agents in advanced cholangiocarcinoma, and further study seems to be needed.

4.2. Second-line chemotherapy

There was not enough evidence about efficacy of second-line chemotherapy for advanced chemotherapy. In a systematic review of second-line chemotherapy in advanced biliary cancer including 25 studies, 14 phase II clinical trials, 9 retrospective analyses, and 2 case reports evaluate the level of evidence for the use of second-line chemotherapy. A total of 761 patients were evaluated, the mean OS was 7.2 months, and the mean progression-free survival, and response and disease control rates were 3.2 months and 7.7 and 49.5%, respectively. In conclusion, there is insufficient evidence to recommend a second-line chemotherapy schedule in advanced biliary tract cancer [57]. Still, the efficacy of second-line chemotherapy for advanced cholangiocarcinoma is not definite. Further prospective randomized trials are needed to develop evidence of second-line chemotherapy for advanced cholangiocarcinoma.

4.3. Guideline recommendation for palliative chemotherapy

The National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) suggest guidelines for chemotherapy in advanced biliary tract cancer.

NCCN guidelines recommend gemcitabine and cisplatin combination therapy as first-line chemotherapy with a category 1 recommendation for patients with advanced biliary tract

cancer [22]. Gemcitabine-based and fluoropyrimidine-based combination chemotherapies are other options with a category 2A recommendation. Based on the results of phase II trials, gemcitabine with oxaliplatin or capecitabine; capecitabine with cisplatin or oxaliplatin; fluorouracil with cisplatin or oxaliplatin; and single-agent fluorouracil, capecitabine, and gemcitabine are included. Second-line chemotherapy is not recommended due to insufficient evidence of the efficacy. In unresectable but nonmetastatic disease, fluoropyrimidine chemoradiation can be another option. In addition, patients with intrahepatic cholangiocarcinoma, locoregional therapy such as external beam radiotherapy, and arterially directed therapy can be tried with a category 2B recommendation.

ESMO clinical practice guidelines suggest a combination therapy for performance score (PS) 0–1 patients and monotherapy for PS 2 patients with advanced cholangiocarcinoma [23]. According to the guidelines, cisplatin/gemcitabine is the reference regimen for good PS patients, and oxaliplatin may be substituted for cisplatin with concern about renal function. For PS 2 patients, gemcitabine monotherapy may be considered. And, second-line chemotherapy and targeted therapies are not recommended due to lack of evidence. Radiotherapy may be considered in patients with localized disease, and radioembolization may be considered in inoperable intrahepatic cholangiocarcinoma.

5. Future directions

5.1. Precision medicine

Personalized therapy is noticed in recent periods including target therapy and immunotherapy, in addition to systemic chemotherapy or chemoradiation for cholangiocarcinoma. Understanding of the molecular pathways associated with development and progression of cholangiocarcinoma may help identify novel biomarkers and develop potential therapeutic targets. On the basis of the development of gene sequencing technic, it is expected that precise medicine will be possible by judging the presence or absence of a specific gene expressed in a patient and selecting a therapeutic drug according to gene expression.

So far, most of previous studies have studied cholangiocarcinoma and gallbladder cancer as a group of biliary tract cancers; however, recent studies revealed that molecular profiling of cholangiocarcinoma is different from gallbladder cancer. Furthermore, several studies reported that intrahepatic and extrahepatic cholangiocarcinomas have different molecular features. Jusakul et al. reported the research combining whole-genome sequencing and epigenomic analysis of cholangiocarcinoma with 489 patients from 10 countries [58]. In the study, cholangiocarcinoma was subgrouped into four clusters according to their molecular features. Cluster 1 comprised mostly fluke positive tumors with enrichment of ARID1A and BRCA1/BRCA2 mutations. Cluster 2 was characterized by a mix of fluke positive and negative tumors with upregulated CTNNB1, WNT5B, and NKT1. Clusters 1 and 2 were enriched in TP53 mutation and ERBB2 gene expression. Clusters 3 and 4 were mostly fluke negative tumors, and cluster 3 exhibited specific upregulation of immune checkpoint genes, PD-1, PD-L2, and BTLA. Cluster 4 had BAP1, IDH1/2 mutations, and FGFR alterations.

Anatomical classification of cholangiocarcinoma was associated with clusters. Clusters 1 and 2 were enriched in extrahepatic tumors, whereas clusters 3 and 4 consisted almost of intrahepatic tumors. Moreover, intrahepatic cholangiocarcinoma was more frequently mutated in BAP1 and KRAS. Clinically, each clusters had different overall survivals; clusters 3 and 4 had significantly better overall survival than clusters 1 and 2. These findings suggest that heterogenic clinical features of cholangiocarcinoma were also based on genetic and epigenetic variance of tumors, and further studies have to focus on classifying subgroups according to treatment strategy and identifying novel therapeutic targets for personalized therapy.

5.2. Identifying novel biomarkers as therapeutic targets

To establish reliable strategy for precision medicine, it is important to identify novel molecular pathways and develop them as therapeutic targets. Recent studies developed growth factor receptors and signaling pathways as targets of cholangiocarcinoma. As mentioned above, the EGFR/VEGF inhibitors and multi-kinase inhibitors have been evaluated to be treatment options. Other promising signaling pathways associated with cholangiocarcinoma, such as RAS/RAF/MEK and PI3K/AKT/mTOR pathways, are also being studied to be another candidate of target agents. Clinical trials and researches are needed to find new target and evaluate efficacy of novel target agents. Big data analysis and artificial intelligence technologies are expected to reduce the time and effort required to set new molecular targets.

5.3. Immunotherapy

Advances in knowledge of cancer immunology provide opportunity of immunotherapy as a new therapeutic option for cholangiocarcinoma. Immunotherapy strengthens the immune system of patients to struggle against cancer by the concept of personalized vaccination, adoptive immunotherapy, or immune checkpoint inhibitor therapy. One of the immune checkpoint inhibitors, pembrolizumab, which is a blocker of programmed cell death 1 (PD-1) pathway and its ligands (PD-L1 and PD-L2), has been reported as a possible promising antitumor agent in patients with advanced biliary tract cancer in the interim results of the clinical trial, KEYNOTE-028. In the study, objective response rate was 17% (four has partial response and four had stable disease) [59]. In addition to the immune checkpoint inhibitor, NK cell, T cell, and dendritic cell-based therapies have been tried to treat cholangiocarcinoma. In the future, immunotherapy might be a new treatment option of biliary cancer treatment.

5.4. Ongoing clinical trials

Although there are no clear results yet, efforts to find new effective chemotherapy regimen for cholangiocarcinoma are continuing. There are several interesting ongoing clinical trials of chemotherapy for cholangiocarcinoma.

For the first-line chemotherapy for advanced cholangiocarcinoma, a phase III study comparing gemcitabine plus cisplatin/S1 combination to gemcitabine plus cisplatin combination is

under investigation (NCT02182778). For the second-line chemotherapy for advanced disease, a phase III trial of mFOLFOX regimen comparing to the best supportive care is ongoing (ABC-06 study, NCT01926236), and another phase III trial is trying capecitabine with varlitinib, an inhibitor of tyrosine kinases—EGFR, HER2, and HER4—compared to capecitabine alone (TreeTopp study, NCT03093870), Also, there is a phase III trial of adjuvant chemotherapy after curative resection with gemcitabine and cisplatin compared to observation alone (ACTICCA-1 trial, NCT02170090).

In addition to these phase III trials, various phase II/phase II trials are underway and expected to report encouraging results in the near future.

5.5. Other challenges

Overcoming disease heterogeneity is another important issue for physicians and researchers. As we discussed, biliary tract cancers have many subgroups according to anatomy and molecular features. In addition to relative rarity of cholangiocarcinoma, this heterogeneity has made clinical trials be small size and segmental. It is very difficult to draw integrated results from individual studies due to these heterogeneity characteristics of cholangiocarcinoma. In the future, it will be necessary to carry out multicenter and international cooperation to conduct large-scale clinical trials with subgroups sharing homogeneous characteristics.

Sample acquisition is one of the challenging tasks in pancreatobiliary tumor. If the future of technology including artificial intelligence allows us to perform more accurate sample acquisition technics or on-site mutation analyses easily, there will be significant benefits for diagnosis and treatment for these fatal diseases. And, established preclinical models need to identify new biomarkers and predict treatment response to chemotherapy. In addition to animal model, in vitro humanlike cell culture methods, such as organoid model or conditionally reprogrammed cell culture, are now being actively studied. These efforts will lead us to the era of precision medicine.

6. Summary and conclusion

Cholangiocarcinoma is a rare malignant tumor that originates from the epithelial cells of the bile duct system. While only surgical resection can provide a cure, most of cholangiocarcinomas are detected at inoperable stage and associated with poor prognosis. Moreover, cholangiocarcinoma has high recurrence rate, even after curative surgery.

Adjuvant chemotherapy is effective in patients with cholangiocarcinoma after curative surgery, especially with lymph node-positive and resection margin-positive disease. Although there are limited clinical trial data to establish a standard chemotherapy regimen for cholangiocarcinoma after surgery, current recommended regimens are fluoropyrimidine-based or gemcitabine-based chemotherapies.

Palliative chemotherapy has an important role in the treatment of advanced and recurrent cholangiocarcinoma. According to the results of randomized controlled phase III trial,

gemcitabine plus cisplatin combination became the standard treatment option for first-line chemotherapy of advanced and metastatic cholangiocarcinoma. Gemcitabine-based or fluoropyrimidine-based combination chemotherapies can be other options. The efficacy of second-line chemotherapy is not definite until now.

Precision medicine is noticed in recent periods in addition to cytotoxic systemic chemotherapy or chemoradiation. Identify novel therapeutic targets based on next-generation sequencing technology, and immunologic assessment is actively taking place. In the future, anticancer therapy of cholangiocarcinoma will develop to identify specific genes expressed in individual patients and provide personalized therapies accordingly.

Conflict of interest

There is no conflict of interest to declare.

Author details

Jung Hyun Jo and Si Young Song*

*Address all correspondence to: sysong@yuhs.ac

Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

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