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TOPIC HIGHLIGHT

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Chemotherapy for cholangiocarcinoma: An update

Natalia Ramírez-Merino, Santiago Ponce Aix, Hernán Cortés-Funes

Natalia Ramírez-Merino, Santiago Ponce Aix, Hernán Cortés-Funes, Department of Medical Oncology, Clinica La Luz, 28003 Madrid, Spain
Author contributions: All the authors contributed equally to this manuscript.
Correspondence to: Dr. Natalia Ramírez-Merino, Department of Medical Oncology, Clinica La Luz, C/ General Rodrigo 8, 28003 Madrid, Spain. narame2@gmail.com
Telephone: +34-91-620728724 Fax: +34-91-620728724
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Abstract

Cholangiocarcinomas (bile duct cancers) are a heterogeneous group of malignancies arising from the epithelial cells of the intrahepatic, perihilar and extrahepatic bile ducts. Patients diagnosed with cholangiocarcinoma must be evaluated by a multidisciplinary team and be treated with individualized management. First of all, it is very important to define the potential resectability of the tumor because surgery is the main therapeutic option for these patients. Overall, cholangiocarcinomas have a very poor prognosis. The 5-year survival rate is 5%-10%. In cases with a potentially curative surgery, 5-year survival rates of 25%-30% are reported. Therefore, it is necessary to increase the cure rate from surgery, exploring the survival benefit of any adjuvant strategy. It is difficult to clarify the role of adjuvant treatment in localized and locally advanced cholangiocarcinomas. There are limited data and the role of adjuvant chemotherapy/chemoradiation in patients with resected biliary tract cancer is poorly defined. The most relevant studies in the adjuvant setting are one from Japan, the well known ESPAC-3 and BILCAP from the United Kingdom and a meta-analysis. We show the results of these trials. According to medical oncology guidelines, postoperative adjuvant therapy is widely recommended for all patients with intrahepatic or extrahepatic cholangiocarcinoma who have microscopically positive resection margins, as well as for those with a complete resection but node-positive disease. Clinical trials are ongoing. The locally advanced cholangiocarcinoma setting includes a heterogeneous mix of patients: (1) patients who have had surgery but with macroscopic residual disease; (2) patients with locally recurrent disease after potentially curative treatment; and (3) patients with locally unresectable disease at presentation. In these patients, surgery is not an option and chemoradiation therapy can prolong overall survival and provide control of symptoms due to local tumor effects. Nowadays, no neoadjuvant therapy can be considered a standard approach for the treatment of patients with cholangiocarcinoma. There are promising results and randomized trials are needed in patients with a metastatic cholangiocarcinoma. In systemic therapy, no single drug or combination has consistently increased median survival beyond the expected 8-12 mo. It is always recommended that patients enrol in clinical trials. Clinical trials have shown that the more standard chemotherapy for a first line regimen of gemcitabine plus cisplatin (or oxaliplatin as a potentially better tolerated agent) is superior to gemcitabine alone. Leucovorin-modulated 5-fluorouracil, capecitabine monotherapy or single agent gemcitabine are reasonable options for patients with a borderline performance status. After progression in patients with an adequate performance status, active regimens that could be considered include gemcitabine plus capecitabine, or erlotinib plus bevacizumab, for second line treatment.

Key words: Chemotherapy; Cholangiocarcinoma; Review; Oncology; Gemcitabine

Core tip: Cholangiocarcinomas (bile duct cancers) are an heterogeneous group of malignancies arising from the epithelial cells of the intrahepatic, perihilar and extrahepatic bile ducts. Leucovorin-modulated 5-fluorouracil, capecitabine monotherapy or single agent gemcitabine are reasonable options for patients with a borderline performance status. After progression in patients with an adequate performance status, ac-

tive regimens that could be considered for second line treatment include gemcitabine plus capecitabine or erlotinib plus bevacizumab.

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INTRODUCTION

Cholangiocarcinomas (bile duct cancers) are malignancies arising from the epithelial cells of the intrahepatic, perihilar and extrahepatic bile ducts.

Bile duct cancers are a heterogeneous group. Overall, cholangiocarcinomas have a very poor prognosis[1]. The 5-year survival rate is 5%-10%. In cases which undergo a potentially curative surgery, the reported 5-year survival rates are 25%-30%[2,3]. In metastatic disease, no single drug or combination has consistently increased median survival beyond the expected 8-12 mo. Different outcomes present depending on the specific location. Other prognosis factors to consider are: perihilar had particularly poor prognosis; margin status; vascular invasion; lymph node metastases; transmural extension to the gallbladder; hepatic venous invasion; histology (papillary ones have a better prognosis); gender (female is better); albumin level (< 3 g/dL is adverse); bilirubin level (> 10 g/dL is adverse)[4,5].

TREATMENT OF LOCALIZED CHOLANGIOCARCINOMAS: ROLE OF ADJUVANT TREATMENT

Patients diagnosed with cholangiocarcinoma must be evaluated by a multidisciplinary team and be treated with individualized management.

First of all, it is absolutely vital to assess the potential resectability of the tumor since surgery represents the main therapeutic option for these patients. Even in patients who undergo complete surgical resection, prognosis is poor and relapses are frequent. The most common relapse pattern is local; distant metastases are less common but not rare, typically a hepatic or peritoneal recurrence[6].

So, it is necessary to increase the cure rate from surgery, exploring the survival benefit of any adjuvant strategy. Postoperative adjuvant therapy is widely recommended for all patients with intrahepatic or extrahepatic cholangiocarcinoma who have microscopically positive resection margins, as well as for those with a complete resection but node-positive disease.

The role of adjuvant chemotherapy/chemoradiation in patients with resected biliary tract cancer is poorly defined. Although it is widely used and recommended in guidelines from medical oncologist expert groups, the survival benefit of any adjuvant strategy has never been proven in specifically designed randomized clinical trials. Most of the recommendations are primarily based on practice patterns at some institutions and on retrospective studies from single center experiences[7,8]. There are limited data from multiple retrospective series and small phase Ⅱ trials from single institutions, but most of these studies are not randomized and with heterogeneous patient populations often combine gallbladder cancers with pancreatic cancers with intrahepatic and extrahepatic cholangiocarcinomas.

The optimal treatment strategy in the adjuvant setting has not been determined. There are no randomized phase Ⅲ clinical trial data to support a standard adjuvant regimen. There are phase Ⅱ trials that support the following regimens: gemcitabine/cisplatin; gemcitabine/oxaliplatin; gemcitabine/capecitabine; capecitabine/cisplatin; capecitabine/oxaliplatin; 5-fluorouracil (5-FU)/oxaliplatin; 5-FU/cisplatin; and for monotherapy with the single agents gemcitabine, capecitabine and 5-FU[9,10].

Following complete surgical resection of intrahepatic or extrahepatic cholangiocarcinoma, postoperative adjuvant therapy is widely recommended for all patients who have microscopically positive resection margins and for all those who have node-positive disease. This is the recommended management suggested in guidelines from expert groups but the actual survival benefit of any adjuvant strategy for cholangiocarcinomas has not been proven in well-designed randomized trials. There are limited data from multiple retrospective series that suggest superior outcomes for patients with postoperative chemoradiotherapy compared to historical series of patients who did not undergo the treatment[11,12].

In a recent retrospective review of the period of 1995-2005 at a single institution, of the patients treated for biliary tract cancer, only 6.5% received adjuvant chemotherapy alone and another 6.5% received chemoradiation[13]. In another retrospective analysis which used the Surveillance Epidemiology and End Results (SEER) database to investigate patients with gallbladder cancer from 1992-2002, only 17% of the 2325 patients in the surgical cohort received adjuvant chemoradiation[14].

There are few studies that evaluate the use of adjuvant chemotherapy alone in patients with biliary tract cancer. Some groups[15] have reviewed the available data on both chemotherapy and targeted therapies for biliary carcinoma and, with conventional chemotherapy, a response rate ranging from 10% to 40% has been reported.

There are other studies: one from Japan, the well-known European Study Group for Pancreatic Cancer-3 and BILCAP from the United Kingdom and a meta-analysis. The first is a single multi-institutional randomized trial from Japan which compared postoperative chemotherapy [two courses of mitomycin C plus infusional 5-FU, followed by prolonged oral administration of 5-FU until tumor progression] *vs* surgery alone in 508 patients with resected pancreatobiliary malignancies, 139

were cholangiocarcinomas. Lymph node metastases were present in 84% and 88% of the patients randomly assigned to chemotherapy and surgery alone, respectively. In the subset of patients with bile duct cancer, 5-year overall survival (5yOS) was not significantly better with chemotherapy (27% *vs* 24%). When the results were stratified according to surgical margins, chemotherapy did not significantly improve outcome in patients undergoing non curative resection (5yOS: 8% *vs* 16%), while there was a statistically non significant trend towards better 5yOS among patients with a potentially curative resection (41% *vs* 28%)[16].

Secondly, the European Study Group for Pancreatic Cancer-3 trial, the largest randomized trial was conducted in patients with resected periampullary adenocarcinomas. Four hundred and twenty-eight patients with periampullary malignancies (96 bile ducts) were randomly assigned to one of three arms: observation, 6 mo of leucovorin-modulated FU or 6 mo of single agent gemcitabine. The use of adjuvant treatment was associated with a potential advantage but was not statistically significant (median 43 mo *vs* 35 mo, HR 0.86, 95%CI: 0.66-1.11), but multivariate analysis, correcting for prognosis factors, found a statistically significant survival benefit for chemotherapy, specifically for gemcitabine, and with a better safety profile. These results must be considered hypothesis generating for further studies[17].

The other important study from the United Kingdom is the BILCAP study[18]. BILCAP is a multi-center prospective, randomised phase Ⅲ trial which is trying to examine the role of adjuvant chemotherapy with oral fluoropyrimidine (capecitabine) in patients following potentially curative surgical resection of a biliary tract cancer. Since 2006, patients in England and Wales with a macroscopically complete surgical resection are randomised to receive either adjuvant chemotherapy with capecitabine or observation. BILCAP is the most successful adjuvant study in biliary tract cancer and is on target to complete accrual early in 2013.

The meta-analysis includes the Japanese trial, two SEER registry analyses and 17 retrospective series, which includes 6712 patients, of whom 1797 received some form of adjuvant therapy. There were 8 studies of radiotherapy (RT) plus chemotherapy, 3 of chemotherapy alone, and 9 of RT alone. Only one study included intrahepatic cholangiocarcinoma. In this meta-analysis, the improvement in five year survival with any adjuvant therapy was not statistically significant [pooled odds ratio (OR) = 0.74, 95%CI: 0.55-1.01] compared with surgery alone. The results were similar when gallbladder and bile duct cancers were analyzed independently. However, the survival benefit from adjuvant therapy was statistically significant when the data from the two large registry series (n = 1233 patients) were excluded (OR = 0.53, 95%CI: 0.39-0.72). The benefits of adjuvant therapy were modality-dependent. In a combined analysis of gallbladder and bile duct cancers, there was a significant survival benefit for chemotherapy (OR = 0.39, 95%CI: 0.23-0.66) and chemoradiotherapy (OR = 0.61, 95%CI: 0.38-0.99) but not RT alone (OR = 0.98, 95%CI: 0.67-1.43). Pooled data from nine studies, in which at least 50% of the patients had nodal or margin positivity, confirmed a statistically significant overall survival advantage for any adjuvant therapy in node-positive disease (OR = 0.49, 95%CI: 0.30-0.80). The majority of these patients (77%) had received chemotherapy alone, while the remainder underwent chemoradiotherapy. Similarly, a significant benefit for any adjuvant therapy was shown for patients with margin-positive disease (OR = 0.36, 95%CI: 0.19-0.68)[19].

While this analysis supports current practice (*i.e.*, adjuvant therapy for high risk subgroups with bile duct cancer), it does not resolve the question of the best treatment strategy for high risk patients or adequately address the benefit of adjuvant therapy for patients with low risk (*i.e.*, node negative) disease.

GUIDELINE RECOMMENDATIONS

The National Comprehensive Cancer Network

For extrahepatic cholangiocarcinoma: For patients with resected, margin-negative extrahepatic cholangiocarcinoma with negative regional nodes, observation, fluoropyrimidine or gemcitabine-based chemotherapy or fluoropyrimidine-based chemoradiotherapy are acceptable options; for patients with carcinoma *in situ* at the margins or positive margins with invasive disease, fluoropyrimidine-based chemoradiotherapy followed by additional fluoropyrimidine or gemcitabine chemotherapy; for positive regional lymph nodes, fluoropyrimidine or gemcitabine-based chemotherapy[20].

For intrahepatic cholangiocarcinoma: For no residual local disease, no adjuvant therapy recommendations are made. For patients with positive margins, options include re-resection, ablation, fluoropyrimidine or gemcitabine-based chemoradiotherapy, or fluoropyrimidine or gemcitabine-based chemotherapy.

Guidelines from the European Society of Medical Oncology

For treatment of either intrahepatic or extrahepatic cholangiocarcinoma, the following are suggested: supportive care or palliative chemotherapy and/or radiotherapy after a non curative resection and consideration of postoperative chemoradiotherapy as an option after complete surgical resection[21].

Efforts should also be made to conduct randomized clinical trials in which the individual disease entities are evaluated separately. They are desperately needed in this area and several are now ongoing. Clinical trial participation is especially encouraged.

NEOADJUVANT THERAPY

Nowadays, no neoadjuvant therapy can be considered a standard approach for the treatment of patients with

cholangiocarcinoma; usually, they are patients with jaundice and a poor functional status at presentation and where a neoadjuvant strategy of preoperative chemoradiotherapy to convert to a potentially resectable disease is difficult. However, there are promising results that suggest the potential benefit of this approach for selected patients in the following small reports.

In an early series of nine (out of a total of 91) patients with extrahepatic cholangiocarcinoma who underwent preoperative chemoradiotherapy prior to exploration, three had a pathological complete response while the remainder showed different degrees of histological response to treatment. Margin negative resections were possible in all nine patients compared to only half of those who did not receive neoadjuvant therapy[22]. The benefit of neoadjuvant chemoradiotherapy was also suggested in a report of 45 patients undergoing concurrent chemoradiotherapy in resected extrahepatic cholangiocarcinoma, of whom 12 were treated neoadjuvantly. Three had a complete pathological response and 11 were able to undergo a complete (R0) resection. Despite having more advanced disease at presentation, patients who received neoadjuvant chemoradiotherapy had longer five year survival (53% *vs* 23%) and rates of grade 2 to 3 surgical morbidity were no higher (16% *vs* 33%) compared with those treated in the postoperative setting[23]. These are promising results that support the need for randomized trials to test this strategy of preoperative chemoradiotherapy.

TREATMENT OF LOCALLY ADVANCED CHOLANGIOCARCINOMA

The term "locally advanced cholangiocarcinoma" includes a heterogeneous mix of patients: patients who have had surgery but with macroscopic residual disease; patients with locally recurrent disease after potentially curative treatment; patients with locally unresectable disease at presentation.

Between 50% and 90% of patients with cholangiocarcinoma present with locally unresectable disease. The prognosis for patients with locally unresectable or recurrent disease is very poor, typically measured in months. The goals of palliative therapy are relief of symptoms (pain, pruritus, jaundice) and improvement in quality of life. There is no role for tumor debulking in these cases. In this setting, chemoradiation therapy can prolong overall survival and provide control of symptoms due to local tumor effects.

The optimal regimen remains uncertain but expert groups suggest fluoropyrimidine or gemcitabine based chemotherapy, like the regimens for advanced disease. In some centers, with its convenience, capecitabine 825 mg/m^2 twice daily during the 5 wk of RT, or even weekly infusional 5-FU (225 mg/m^2 daily for 5 wk of RT) is used, following an additional 4 mo of chemotherapy alone with capecitabine alone 1000 mg/m^2 twice daily for 14 d of every 21 d. In cases of very aggressive tumors or with multiple positive nodes, some prefer the use of gemcitabine plus oxaliplatin concurrent with radiotherapy.

There are three different modalities included in radiotherapy: (1) external beam irradiation (EBRT) delivered either by conventional approaches or with conformal treatment planning techniques; (2) brachytherapy with iridium-192; and (3) stereotactic radiotherapy.

Conventional dose EBRT (with or without systemic chemotherapy) may relieve pain and contribute to biliary decompression. At one year, 60%-75% of patients are free of locoregional disease progression and median survival approximates 7 to 12 mo[24]. However, local failure remains the first site of disease progression in 50%-75% of cases. Higher dose RT approaches that use either a combination of transcatheter brachytherapy plus EBRT, three-dimensional conformal radiation therapy or intensity modulated radiation therapy with or without chemotherapy may be associated with better local control and possibly prolonged survival[25]. Technical advances over the past few years have created the ability to deliver more precise, highly conformal radiation treatment to the tumor, maximally sparing adjacent normal tissues. The enhanced capability to spare such normal tissues now permits the safe delivery of a single or limited number of high dose radiation fractions to a target, whereas in the past, small fractions of daily radiation were typically used to spare normal tissues. Approaches such as these are referred to as stereotactic body radiotherapy or stereotactic body radiosurgery, although many current approaches no longer utilize an external stereotactic localization method. Experience is limited. One report included 27 patients with unresectable cholangiocarcinoma who underwent stereotactic body radiotherapy (45 Gy in three fractions) as the sole form of therapy[26]. At a median follow-up of 5.4 years, only two were still alive and the median progression-free and overall survival was 6.7 and 10.6 mo, respectively. While local control was maintained in 84% of patients at one year, six had severe duodenal/pyloric ulceration and three developed duodenal stenosis.

No randomized trial has compared any of these newer radiotherapy techniques to conventional EBRT alone or fluoropyrimidine-based chemoradiotherapy using conventional fractionation. Furthermore, the possibility of higher rates of long-term toxicity[27] has tempered enthusiasm for these approaches.

SYSTEMIC THERAPY FOR ADVANCED CHOLANGIOCARCINOMA

Several regimens of chemotherapy are active for the treatment of advanced cholangiocarcinoma. Evidence is inconsistent because the literature regarding treatment results with specific regimens is limited because most series are small and reports consist of a mix of bile duct cancers, gallbladder cancer, ampullary cancer and either pancreatic or hepatocellular cancers. The most active agents are 5-FU, gemcitabine, cisplatin and oxaliplatin.

In patients with advanced biliary tract cancer, the

survival benefit for chemotherapy over best supportive care alone was suggested in a trial that randomly assigned 90 patients with advanced pancreatic or biliary cancer (37 with bile duct cancer) to 5-FU-based systemic chemotherapy with leucovorin and etoposide *vs* best supportive care alone (median survival 6 *vs* 2.5 mo, respectively)[28].

Chemotherapy combinations and single agents have been evaluated in clinical studies in the metastatic setting, as reviewed by Hezel *et al*[10].

Chemotherapy combinations with activity demonstrated in phase Ⅱ clinical trials include: gemcitabine plus cisplatine; gemcitabine plus capecitabine; gemcitabine plus oxaliplatin; capecitabine plus oxaliplatin; capecitabine plus cisplatine; and 5-FU plus cisplatine.

It is known that gemcitabine is the main cytostatic for bilio-pancreatic cancer. Additional support for gemcitabine as an anchor drug for the treatment of advanced biliary cancer comes from these results: Firstly, a recent pooled analysis of 104 trials of patients with advanced biliary tract cancers that showed that the subgroup receiving a combination of gemcitabine and platinum-based agents had the greatest benefit[29]. Then, a retrospective review of 304 patients with advanced cholangiocarcinoma who received gemcitabine, a cisplatin-based regimen or a fluoropyrimidine-based regimen, showing that patients receiving a gemcitabine-based regimen had a lower risk of death[30].

Most importantly, the superiority of the combination gemcitabine-cisplatin regimen is shown in the recently published ABC Trial. A multicenter, randomized controlled phase Ⅲ study, which enrolled 410 patients with locally advanced or metastatic cholangiocarcinoma (n = 242), gallbladder (n = 148) and ampullary (n = 20) cancers, demonstrated that the combination of gemcitabine and cisplatin improved overall survival and progression free survival by 30% more than gemcitabine alone. Median overall survival was 11.7 *vs* 8.1 mo (HR 0.64, 95%CI: 0.52-0.80) and median progression free survival was 8.0 mo *vs* 5.0 mo (HR 0.63, 95%CI: 0.51-0.77), both in favor of the combination arm. Based on these results, the combination gemcitabine plus cisplatin is considered as the standard of care as first-line chemotherapy for biliary tract cancer treatment[31].

NEW AGENTS COMBINATION

There are currently several trials investigating the role of molecularly targeted therapies in biliary tract cancers. Combinations with TKI antiEGFR such as erlotinib, other antiEGFR such as cetuximab, antiangiogenics such as bevacizumab *etc.* are being examined. Although encouraging data are emerging with the use of targeted therapies, further efforts and additional data with randomized trials are needed to improve treatment options for patients.

CONCLUSION

In conclusion, patients with localized and locally advanced cholangiocarcinomas must be treated in a multidisciplinary team. Surgery is the main therapeutic option for these patients but it is necessary to improve results and survival benefit. It is difficult to clarify the role of adjuvant treatment. In medical oncology guidelines, postoperative adjuvant therapy is widely recommended for all patients with intrahepatic or extrahepatic cholangiocarcinoma who have microscopically positive resection margins, as well as for those with a complete resection but node-positive disease. There are clinical trials ongoing. In systemic therapy, gemcitabine plus cisplatin has been shown to be superior to gemcitabine alone, but this regimen has not been compared head to head with other gemcitabine-based combinations. It is always recommended that patients enrol in clinical trials. Nevertheless, if a patient is not a candidate for a clinical trial or if one is not available, we suggest gemcitabine plus cisplatin (or oxaliplatin as a potentially better-tolerated agent) for a first line regimen for patients with a good performance status. Leucovorin-modulated 5-FU, capecitabine monotherapy or single agent gemcitabine are reasonable options for patients with a borderline performance status. After progression in patients with an adequate performance status, active regimens that could be considered include gemcitabine plus capecitabine or erlotinib plus bevacizumab for second line treatment.

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