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Future directions in the treatment of cholangiocarcinoma



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A B S T R A C T

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Cholangiocarcinoma (CCA) comprises a heterogeneous group of cancers with pathologic features of biliary tract differentiation, and is best classified anatomically as intrahepatic CCA (ICC), perihilar (pCCA), or distal (dCCA) CCA.

They represent a clinically and genetically diverse collection of cancers. Surgical resection represents the only curative modality for CCA, although there are encouraging data with liver transplantation for early stage pCCA. There is no established adjuvant therapy for CCA. Unfortunately, most patients with CCA will present with unresectable or metastatic disease with poor prognosis. Currently the combination of gemcitabine and cisplatin remains the standard therapy for advanced CCA. No second line therapy has definitely demonstrated improved survival benefits. Development of molecularly targeted therapies in advanced CCA remains challenging. However, recent efforts with targeted and whole exome sequencing have defined the landscape of mutations underlying CCA, particularly ICC. The identification of novel molecular signatures in CCA coupled with molecularly targeted therapy development provides the potential for developing novel therapeutic options in this intractable disease.

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Introduction

Cholangiocarcinoma (CCA) comprises a heterogeneous group of cancers with pathologic features of biliary tract differentiation, and is best classified anatomically as intrahepatic CCA (ICC), perihilar (pCCA), or distal (dCCA) CCA [1]. They represent a clinically and genetically diverse collection of cancers [2]. CCA is characterized by early lymph node and distant metastases and as a result, only ten percent of patients present with early-stage disease and are considered candidates for surgical resection, which offers the only chance for cure. In selected centers, liver transplantation may be considered as an option for early-stage pCCA. There is no established adjuvant therapy for CCA. Unfortunately, most patients with CCA will present with unresectable or metastatic disease with poor prognosis with a median survival of approximately one year. Currently the combination of gemcitabine and cisplatin remains the standard therapy for advanced CCA [3]. No second line therapy has definitely demonstrated improved survival benefits. Development of molecularly targeted therapies in advanced CCA remains challenging. However, recent efforts with targeted and whole exome sequencing have defined the landscape of mutations underlying CCA, particularly ICC. The identification of novel molecular signatures in CCA coupled with the arrival of new targeted agents holds promise for developing novel therapeutic options in this intractable disease. Here the author will attempt to review the current treatment landscape and share his view on future treatment directions for CCA.

Standard treatment options for CCA

Table 1 outlines the currently available treatment options for CCA. Of these, surgical resection represents the mainstay of curative intent treatment for CCA and is associated with improved survival in selected patients [4,5]. The five-year survival rate with surgery varies depending on the specific anatomic locations and is in the range 30–35% for ICC and 35–50% for pCCA in the setting of R0 resection [5–7]. Liver transplantation represents another potentially curative treatment modality in CCA. In contrast to the experience in hepatocellular carcinoma (HCC), liver transplantation with CCA still has relatively limited experience with selective centers and it is mainly limited to early stage perihilar CCA. It is generally reserved for highly selected patients (3 cm or less in radial diameter) who are not eligible for resection and involves the use of neoadjuvant 5-FU based chemoradiation, endoluminal brachytherapy boost, followed by capecitabine until liver transplantation [8].

For the majority of the patients who present with locally advanced or metastatic disease, systemic chemotherapy remains the mainstay treatment. Convincing evidence from randomized trials supports the use for gemcitabine with cisplatin as first line treatment in advanced and metastatic CCA. The UK National Cancer Research Institute Advanced Biliary Cancer (ABC-02) phase III study enrolled 410 patients with locally advanced or metastatic CCA (n = 242), gallbladder cancer (n = 148), or ampullary

Table 1

Standard treatment options for cholangiocarcinoma.

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- Curative treatments
 - Surgical resection
 - Liver transplantation: Only for perihilar cholangiocarcinoma
 - Liver directed local-regional therapy-mainly for intrahepatic cholangiocarcinoma
 - Ablation
 - Chemoembolization (TACE)
 - Drug eluting beads TACE
 - Radioembolization with yttrium-90
 - Radiation (stereotactic body radiotherapy, proton etc)
 - Chemoradiation or radiation in the adjuvant setting or for locally advanced unresectable perihilar or distal cholangiocarcinoma
 - Systemic chemotherapy with gemcitabine/cisplatin-standard treatment for unresectable or metastatic cholangiocarcinoma
 - Empiric chemotherapy in patients who failed gemcitabine/cisplatin
 - Clinical trials
 - Symptomatic control for biliary obstruction and pain
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