

Treatment of Advanced Cholangiocarcinoma: Current Status and Future Perspectives

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The aim of this short review is to give an update on standard and prospective treatment concepts in advanced cholangiocarcinoma based on a comprehensive review of the recent literature and guidelines.

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Abstract

Cholangiocarcinoma (CC) is a tumour with a poor prognosis. The treatment of CC is challenging as the tumour is usually diagnosed late and the treatments are not very effective except when complete surgical resection is possible. However in the majority of cases, surgical resection is not possible and palliation is the mainstay of treatment. Currently chemotherapy combining gemcitabine with a platinum agent is the recommended first-line treatment regimen for advanced CC. Since, CCs have only a limited tendency to metastasize locoregional therapy is an interesting approach.

Introduction

Cholangiocarcinoma (CC) is a relatively rare, heterogenous tumour entity with a poor prognosis. It is distinguished by anatomic site and typically classified as either intrahepatic or extrahepatic cholangiocarcinoma. Intrahepatic cholangiocarcinomas (IHCC) are located within the hepatic parenchyma and have also been called "peripheral" CCs. CCs occurring anywhere within the common hepatic duct or the common bile duct are classified extrahepatic cholangiocarcinomas (EHCC). Perihilar CC (also called Klatskin tumour) belongs to the EHCC, and is the most common type, however incidence and mortality rate of IHCCs have increased markedly worldwide.⁽¹⁾

Perihilar or extrahepatic CCs typically present with features of biliary obstruction. Intrahepatic CCs are usually more advanced at presentation. These tumours often present with systemic manifestations of malignancy including malaise, fatigue and weight loss. Some cases are detected incidentally as a result of scans performed for other indications.

Treatment of resectable tumours

Surgical resection offers the only curative option and usually requires a major hepatic resection in addition to resection of actual bile duct cancer. Unfortunately, curative resection is only possible in about 20% of patients because of locally advanced disease, distant metastases or co-morbidity in an elderly population.⁽²⁾

Resection involves a major operative procedure and requires appropriate surgical and anaesthetic experience. Surgical treatment depends on the site and extent of bile duct involvement by tumour. IHCCs are usually treated by resection of the involved segments or lobe of the liver. Distal CCs are managed by pancreatoduodenectomy, as with ampullary or pancreatic head cancer. Major hepatectomy for hilar CCs carries a considerable risk of hepatic insufficiency if there is a small future liver remnant. Portal vein embolisation of the lobe to be removed is a safe method for increasing the future liver remnant and permits curative hepatic resection to be carried out.⁽³⁾ But even after resection, the rate

of recurrence is approximately 60% and the 5-year overall survival (OS) rates are 15-40% for IHCC and 23-50% for EHCC.⁽⁴⁾

Historically, liver transplantation for CC was associated with rapid recurrence of disease and poor survival rates.⁽⁵⁾ However, increasing data suggest that liver transplantation for CC can be successful in rigorously selected patients undergoing neoadjuvant therapy in highly specialised centres.⁽⁶⁾

Adjuvant therapy

Because of the high recurrence rates radiotherapy (RT), radiochemotherapy (RCT) and chemotherapy (CT) alone have been investigated in an adjuvant setting to improve progression free survival. Their role, however, is still undefined, due to the limited number of patients evaluated, the prevalence of retrospective trials and the heterogeneity of stages and types studied.

Treatment of unresectable tumours

Endoscopic stenting

The median survival time of advanced CC undergoing supportive care alone is short.⁽⁷⁾ Effective palliation to relieve the symptoms associated with jaundice and the prevention of biliary tract infection are fundamental goals for most patients with hilar CC. Relief of biliary tract obstruction by endoscopic or percutaneous placement of plastic or metal stents is regarded the optimal first-line palliation as this achieves similar survival to surgical bypass, but less procedure-related morbidity or mortality and at substantially lower costs.⁽⁸⁾

Photodynamic therapy

Photodynamic therapy (PDT) is a relatively new ablative therapy, involving intravenous injection of a photosensitising drug followed by selective irradiation with light of a specific wavelength to initiate localised drug activation, and has been used for palliation in patients with hilar CC. The combination of PDT with biliary stenting was reported to improve the OS of patients with unresectable CCs in two small randomised clinical trials.^(9,10) In contrast to these results, the preliminary data of the UK Photostent-02 trial demonstrated, that patients receiving PDT had no benefit in OS compared to patients treated with endoscopic stenting alone (5.6 vs. 8.5 months).⁽¹¹⁾

However fewer patients in the PDT group received additional palliative chemotherapy.

Chemotherapy

The recently published randomised, controlled phase III ABC-02 study, which enrolled 410 patients with locally advanced or metastatic CC, gallbladder cancer, or ampullary cancer, demonstrated that the combination of gemcitabine and cisplatin improves overall survival and progression-free survival by 30% over gemcitabine alone.⁽¹²⁾ Median OS was 11.7 months and 8.1 months (hazard ratio=0.64; 95% CI, 0.52-0.8; P<0.001), and median progression-free survival was 8.0 months vs. 5.0 months (hazard ratio=0.63; 95% CI, 0.51-0.77; P<0.001), both in favour of the combination arm. Although the rate of neutropenia was higher in the group receiving gemcitabine and cisplatin, there was no significant difference in the rate of neutropenia-associated infections between the two arms.

A Japanese phase II trial of gemcitabine with cisplatin vs. gemcitabine alone found very similar results with median OS of 11.2 months in the combination arm.⁽¹³⁾

Oxaliplatin is widely used in clinical practice instead of cisplatin: the safety profile of the GEMOX regimen (gemcitabine and oxaliplatin) and the good response rates (RR) suggest that this is not a suboptimal treatment when compared to the standard schedule with cisplatin.⁽¹⁴⁾

Based on these results, currently chemotherapy combining gemcitabine with a platinum agent is the recommended first-line treatment regimen for advanced CC.

With respect to second-line palliative therapy, a recent retrospective analysis of 395 patients over 20 years at a single centre showed that after first-line chemotherapy, 25% of patients received a second-line regimen, and only 6% a third-line regimen.⁽¹⁵⁾ Objective response rate (RR) and stable disease with second-line chemotherapy were 9% and 34%, respectively Median PFS and median OS measured from the initiation of second-line chemotherapy was 2.8 and 7.5 months, respectively.

New targeted agents (e.g. anti-angiogenic or EGFR/RAS/RAF/MEK pathway inhibitors) are urgently needed for a more effective therapy. These agents

are currently tested alone, or two of these together, or in combination with cytotoxic chemotherapy in clinical trials.

Locoregional therapies

CCs have only a limited tendency to metastasize, and only one-third of the patients had lymph node, hepatic, or peritoneal metastases at surgery.⁽¹⁶⁾ Therefore, locoregional therapy is an interesting approach for treatment of this tumour.

Radiofrequency ablation (RFA)

Percutaneous image-guided radiofrequency ablation (RFA) is a minimally invasive technique that uses high frequency alternating current to heat tissue to the point of coagulation with the aim of local curation.

A study of 13 patients with 17 primary IHCCs treated with RFA reported a local control rate of 88% at a median follow-up of 19.5 months. Two local failures occurred, both in tumours larger than 5cm in diameter. The median OS after RFA was 38.5 months.⁽¹⁷⁾ Only one major complication (liver abscess) occurred in 17 RFA sessions. Similiary results demonstrated a Chinese non-randomised study of 18 patients.⁽¹⁸⁾

Together, these findings indicate that RFA may provide successful local tumour control in patients with intermediate (3-5m) or small (<3cm) intrahepatic nodules. Tumour size larger than 5cm, tumour geometry, proximity to large intrahepatic vessels and subcapsular location are factors that usually lead to insufficient ablations and significantly influence outcome. To overcome this problem stereotactic RFA may be an applicable technique.⁽¹⁹⁾ However this technique is very complex and may involve major complications.

Transcatheterarterial chemoembolisation (TACE)

Transcatheter arterial chemoembolisation of the liver has been shown to provide durable response in hepatocellular carcinoma.⁽²⁰⁾ This technique utilizes a dual therapeutic approach to target solid tumours - the infusion of multiple chemotherapeutic agents combined with hepatic artery embolisation. Chemoembolisation reduces oxygen and nutrient delivery to the tumour while concurrently providing a 10- to 25-fold increase in local chemotherapy concentration and reducing drug clearance from

the liver. Severe toxicity is limited, as up to 85% of the administered drug is trapped in the liver. This makes the side effect profile of chemoembolisation attractive relative to systemic chemotherapy.

In several series of patients with IHCC TACE, using different chemotherapeutic agents, seemed to be safe and effective with a median OS of approximately 12-26 months⁽²¹⁻²⁵⁾. All studies are limited by a low number of patients, the non-randomised, and partial retrospective design. TACE have been even studied in a adjuvant setting, however with no effect on survival.⁽²⁶⁾

Drug eluting bead (DEB)-TACE

Chemoembolisation with drug-eluting beads combines the drug with the embolisation device by using the embolic device to reduce blood flow to the tumour whilst at the same time eluting a chemotherapeutic agent into the tumour via its own vasculature. Therefore, beads with the capability to elute drugs may offer the possibility to control precisely the release and dose of the chemotherapeutic agent into the tumour bed.

Aliberti et al.⁽²⁷⁾ demonstrated in 11 patients treated with DEB-TACE using doxorubicin a chemotherapeutic agent a median OS of 13 months. In another retrospective study DEB-TACE using irinotecan median OS was comparable to chemotherapy using the GEMOX regimen and even superior to conventional TACE using mitomycin C.⁽²⁸⁾ Further, Poggi et al.⁽²⁹⁾ reported an OS of 30 months in nine patients with intrahepatic CC, treated with a combination of oxaliplatin DEB-TACE and systemic chemotherapy (CHT) with oxaliplatin and gemcitabine. All studies are limited by a low number of patients and the non-randomised design.

Nevertheless, locoregional therapy with TACE, especially DEB-TACE seems to be active, and its combination with systemic CHT seems promising.⁽²⁹⁾ Therefore randomised prospective clinical trials enrolling a larger number of patients need to be carried out, comparing the efficacy of TACE or DEB-TACE using different chemotherapeutic agents (e.g. irinotecan, oxaliplatin, doxorubicin, and mitomycin C) and evaluate the combination of TACE with systemic CHT.

Radiation therapy

Data on external beam radiation therapy (EBRT) are limited. Due to the fact that whole-liver dose of extending 40 Gy often is associated with severe side effects, including life-threatening radiation induced liver disease EBRT is restricted to those patients with a small and focal tumour burden, where a sufficient volume of the liver remains untreated. Through the development of radiation therapy this problem may be overcome using stereotactic body radiotherapy. Barney et al. demonstrated in a study of 10 patients that a dose escalation up to 60 Gy (mean 55 Gy) is feasible and has promising local effects.⁽³⁰⁾ However another study reported of 22% serious gastrointestinal injury mainly biliary stenosis and duodenal/pyloric ulcerations after stereotactic radiotherapy.⁽³¹⁾

Transarterial radioembolisation

Liver tumours are generally radiosensitive and transarterial radioembolisation with yttrium-90 (90Y) microspheres has been demonstrated to be effective in unresectable HCC and metastases of the liver.⁽³²⁾

In contrast to TACE, for intra-arterial radioembolisation to be effective, optimal perfusion and blood flow is required to allow the generation of free radicals by ionisation of water molecules near the tumour cell's DNA. In the presence of normal oxygen tension, permanent DNA damage is caused by one or both DNA strands, and apoptosis is initiated or reproductive death is eventually achieved.

In a series of 24 patients with unresectable IHCC, radioembolisation with 90Y microspheres induced >50% tumour necrosis and 100% tumour necrosis in

77% and 9% of patients respectively, with a median OS of 14.9 months.⁽³³⁾ In another study of 25 patients 90Y radioembolisation achieved in 24% partial remission and in 48% stable disease resulting in a median OS of 9.3 months.⁽³⁴⁾

Conclusion

Most CCs are locally advanced or metastatic disease at the time of diagnosis. Even if it is resectable, long time survival rates are low.⁽⁴⁾ Due to its low incidence and heterogeneity of this cancer, there are few high quality randomised clinical trials. Currently chemotherapy combining gemcitabine with a platinum agent is the recommended first-line treatment regimen for advanced biliary tract cancer.⁽¹²⁾

However, median OS is only approximately one year. Locoregional therapies such as RFA, TACE and transarterial radioembolisation have been shown to be safe and effective in IHCC. Most of these studies are not randomised, often combine gallbladder cancers with intrahepatic and extrahepatic CC, and involve small numbers of patients, making it difficult to draw definitive conclusions. Nevertheless liver directed therapy can make a meaningful contribution as part of oncologic treatment to reduce systemic side effect of CHT and prolong survival in advanced CC.

Therefore randomised prospective clinical trials enrolling a larger number of patients need to be carried out.

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