Cholangiocellular Carcinoma

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Keywords

Cholangiocarcinoma · Biliary tract cancer · Chemotherapy · Targeted therapy

Abstract

Background: Cholangiocarcinomas (CCAs) are aggressive malignancies that display features of biliary differentiation. According to their anatomical location, CCAs are commonly classified as intrahepatic and extrahepatic tumors, the latter entity being further subdivided into perihilar CCAs, also termed as Klatskin tumors, and distal tumors. While a majority of CCAs occur sporadically, established risk factors such as liver fluke infestation or primary sclerosing cholangitis exist. **Summary:** Due to lack of efficient early screening markers, CCAs are frequently diagnosed at an advanced stage when curative surgical resection is not an option. Chemotherapy with gemcitabine and cisplatin is currently the standard palliative treatment that prolongs overall survival by 3.6 months as compared to monotherapy with gemcitabine. For CCA patients who progress under gemcitabine/cisplatin, the paucity of prospective, randomized trials is detrimental, and there is currently no recommended second-line regimen with respect to chemotherapy or loco-regional treatment modalities. Molecular profiling of CCAs supports the implementation of targeted approaches, and it is reasonable that personalized therapy will become a mainstay of CCA treatment. In addition, the advent of immunotherapy holds

considerable promise, yet, similar to targeted treatment, needs to be prospectively evaluated in clinically and genetically thoroughly characterized patients. **Key Points:** (1) CCA is a genetically diverse and highly aggressive malignancy. (2) Gemcitabine in combination with cisplatin or oxaliplatin is the current first-line chemotherapy in non-resectable patients. (3) Loco-regional treatment modalities exist but need to be evaluated in prospective randomized trials in the context of systemic chemotherapy. (4) Targeted therapies in molecularly defined subgroups of patients and immunotherapies alone or in combinations will most likely improve survival in the future.

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Epidemiology and Risk Factors

Cholangiocarcinomas (CCAs) are rare tumors, with an overall incidence of less than 2/100,000 [1]. The epidemiological profiles of CCA subtypes vary significantly, reflecting the exposure to different risk factors and most likely different genetic backgrounds. CCA incidence ranges between 0.1/100,000 in Australia and more than 130/100,000 in parts of Asia [2]. Epidemiological studies looking at the prevalence in different countries and regions have mostly but not uniformly reported a rise in CCA [3–6]. In Germany, mortality of intrahepatic CCA (IH-CCA) has more than tripled between 1998 and 2008. In line with the

increased mortality data, the number of reported cases of IH-CCA also increased between 1970 and 2006 [7].

A vast majority of CCAs (70%) occur sporadically without any apparent cause. However, several risk factors that promote cholangiocarcinogenesis have been identified. In East Asia, infestation with the liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis* by ingestion of raw or pickled fish is a major risk factor [8]. In Western populations, the strongest association has been established for primary sclerosing cholangitis (PSC), with or without accompanying inflammatory bowel disease [9]. Cholangiocarcinogenesis has also been associated with different forms of cholelithiasis and rare congenital anomalies of the bile duct such as Caroli's disease [10, 11]. More recently, hepatitis B and hepatitis C virus infection and infection-associated cirrhosis as well as diabetes and obesity have been shown to increase the risk for CCA development [10, 12–14]. Notably, most of the designated risk factors are associated with recurrent cholangitis and chronic local inflammation, indicating that inflammation acts as an underlying pathogenic mechanism in cholangiocarcinogenesis.

Prevention and Surveillance

Preventive measures are relevant in endemic regions and include health education (routes of parasitic and viral infection), vaccination, and antiviral therapies, as well as avoiding exposure to toxins such as 1,2-dichloropropane. Preclinical studies have shown that COX-2 is implicated in early cholangiocarcinogenesis [15]. Accordingly, regular aspirin intake was associated with a reduced incidence and mortality in various cancer types within observational studies [16]. Specifically, a 2.7- to 3.6-fold decreased risk for CCA was reported in a case-control study, encouraging prospective trials investigating the potential benefit of aspirin in selected risk groups [17].

Surveillance, including imaging and testing of liver enzymes and tumor markers, has been suggested as a suitable method for early cancer detection in high-risk groups, such as patients with PSC. However, recommendations concerning the modality and frequency of screening are inconsistent, and implementation of stratified surveillance standards tailored to the distinct risk groups is warranted [1, 18]. In the absence of established biomarkers, screening efforts in the near future will most likely rely on imaging modalities, specifically ultrasound, and in selected high-risk groups on MRI.

Pathogenesis

The molecular landscape of CCA is highly heterogeneous, and the genetic profiles segregate with the anatomical location, the histological subtype, as well as with the putative pathogenic risk factors. It is increasingly recognized that CCA is not a uniform disease with respect to the cancer cell of origin, and that indeed different liver-resident cells as well as cells lining the biliary tree have the propensity to give rise to specific subclasses of CCA. The heterogeneity of tumor-initiating cells may account for the genetic profiles that diverge across the anatomical and morphological features.

Despite the genetic diversity, a recurrent repertoire of driver genes and potentially targetable lesions exists: indeed, across 239 biliary tract cancers (including 28 gallbladder cancers), 40% of patients harbored targetable lesions [19], indicating targeted therapy will complement therapeutic approaches, yet only in highly stratified patient groups. Key molecular pathways involved in cholangiocarcinogenesis comprise activated RAS- and PI3K signaling, deregulated NOTCH signaling, and loss of Tp53-guided cell cycle control. In addition, the high frequency of inactivating mutations in chromatin remodeling genes (ARID1a, PBRM1, BAP1) as well as recurrent mutations in IDH1 and 2 points towards a crucial role of epigenetic regulation in cholangiocarcinogenesis. Recently, gene fusion events, frequently involving a portion of the tyrosine kinase receptor FGFR2, were identified especially in IH-CCA and represent potential therapeutic targets [20].

A hallmark feature of CCA is the prominent desmoplastic stroma. While our current understanding of the role of the tumor microenvironment is limited, the tumor stroma likely contributes to tumor initiation, progression, and treatment response. A better understanding of the complex crosstalk between tumor cells and stroma cells will be crucial to address the therapeutic promises and perils associated with targeting the tumor stroma.

Surgery and Adjuvant Therapy

Radical resection is the treatment of choice but is feasible only in 25–35% of all patients [21]. Locally advanced or metastatic disease due to late diagnosis precludes curative surgery in the majority of patients, and high recurrence rates even after resection further aggravate the dismal prognosis: in a cohort of 175 extrahepatic CCA patients, the 5-year overall survival (OS) rate following curative resection was 26% [22]. A retrospective analysis

of 221 IH-CCA patients surgically resected in our clinic yielded a 3-year OS rate of 40 vs. 36.4% after R0 and R1 resection respectively [23].

Liver transplantation is no standard therapy for CCA patients but might be a promising option for cure in highly select patients. A recent retrospective study including patients who were first diagnosed with IH-CCA at explant pathology after liver transplantation reported a 5-year recurrence rate of 18% in patients with single tumors ≤ 2 cm, compared to 61% in patients with tumors >2 cm or multifocal disease [24].

Considering the high risk of relapse following surgery, the potential benefit of adjuvant therapies needs to be explored. In a recent meta-analysis of published data, adjuvant chemotherapy appears to be associated with a survival benefit in patients with lymph node-positive disease and adjuvant chemoradiotherapy in patients with microscopically involved margins (R1 resection) [25]. Currently, 3 ongoing phase III trials address the potential benefit of adjuvant treatment following curative resection: the BilCap study in England (comparing capecitabine versus observation) and the PRODIGE-12 study in France (comparing gemcitabine and oxaliplatin versus observation) have completed recruitment and are awaiting data maturation. In Germany, the ACTICCA study comparing gemcitabine and cisplatin versus observation is still recruiting.

Local Therapies

Subclinical or frank cholangitis is associated with increased morbidity and mortality. Efficient endoscopic or percutaneous biliary drainage is not only crucial to enhance prognosis and quality of life but is frequently also a prerequisite for palliative therapy. Local tumor ablation through photodynamic therapy was introduced as a treatment modality in 1991 and improved survival in small clinical trials and retrospective studies compared to best supportive care. Moreover, for patients presenting with liver-confined disease, additional loco-regional therapies are available, including intraductal percutaneous radiofrequency ablation, high-dose-rate brachytherapy, as well as transarterial approaches, such as hepatic arterial infusion chemotherapy, transarterial chemoembolisation, 90Yttrium radioembolisation, and external beam radiation, but most of these treatment modalities were evaluated retrospectively or as single-center studies [26]. The only prospective study, the French FFCD 9902 phase III trial comparing chemoradiotherapy with 5-FU and

cisplatin to gemcitabine and oxaliplatin in patients with locally advanced CCA, was discontinued early because a trend for prolonged survival in the chemotherapy alone arm was observed [27]. Prospective evaluation is clearly required to assess the impact of local therapies on the morbidity and mortality of patients with CCA, specifically in the context of systemic chemotherapy.

Systemic Therapies

CCA is an intrinsically highly chemoresistant malignancy. However, most patients with CCA are eventually bound to receive non-curative treatment. In 2010, the randomized phase III ABC-02 study compared gemcitabine as a single agent to a combination chemotherapy with gemcitabine and cisplatin in 410 patients with locally advanced or metastatic CCA, GBC, or ampullary carcinoma. The median survival was significantly prolonged by 3.6 months in the group that received gemcitabine in combination with cisplatin than with gemcitabine alone, with no overt increase in toxicity [28]. Similar results were observed in a Japanese randomized phase II trial and confirmed in a pooled analysis of both trials [29]. Therefore, the combination of gemcitabine and cisplatin is nowadays the standard first-line treatment for non-resectable CCA. When contraindications, such as renal insufficiency, exist, cisplatin may be replaced by oxaliplatin [30, 31]. Single-agent treatment with gemcitabine is still considered appropriate for elderly or moribund patients. In addition to gemcitabine-based chemotherapy, fluoropyrimidines have shown efficacy in the treatment of CCA [32] and patients with tumor progression under first-line chemotherapy frequently receive a fluoropyrimidine based second-line regime. However, a recent meta-analysis of 14 non-randomized phase II trials concluded that there is insufficient evidence to recommend second-line chemotherapy [33]. To assess whether patients may benefit from second-line mFOLFOX regime compared to best supportive care, the randomized first phase III study ABC06 Trial (NCT01926236) is currently recruiting.

Targeted Therapies

The field of oncology has changed in the last years by the introduction of targeted therapies. Indeed, targeted approaches have revolutionized the treatment of several

tumor entities, such as leukemia, non-small cell lung cancer or melanoma. In CCA, however, the overall success of targeted strategies has been rather modest so far.

Initial promising results from nonrandomized phase II studies triggered a significant interest in targeting the epithelial growth factor receptor. The early enthusiasm, however, was dampened by the recently published phase II study BINGO that concluded that there was no benefit of intensifying gemcitabine and oxaliplatin by the addition of cetuximab [34]. Moreover, the German PICCA study evaluating the efficacy of panitumumab in combination with gemcitabine and cisplatin in KRAS wildtype patients was also negative for the primary endpoint PFS with no improvement of OS. Finally, results from a phase III trial evaluating gemcitabine and oxaliplatin with or without erlotinib in patients with CCA, GBC, or ampullary cancer were similarly disappointing [35].

Proteins of the vascular endothelial growth factor (VEGF) family are well recognized as mediators of angiogenesis and vascular permeability but may have additional pro-tumorigenic effects on immune cells and tumor cells themselves. Studies investigating the VEGF-A antibody bevacizumab, the VEGF inhibitor cediranib and the multikinase inhibitor sorafenib failed to show convincing anti-tumoral activity in CCA both as a single agent as well as in combination therapy [36–38]. Currently, ramucirumab, a VEGFR2-directed monoclonal antibody, is evaluated in a phase-II study in combination with gemcitabine and cisplatin.

Future Directions

The median survival for patients with metastatic CCA with current chemotherapy options is still less than 1 year, highlighting the urgent need to develop more effective systemic treatments. Recent sequencing efforts have shed light on the mutational landscape of CCA, and new molecular classifications provide the groundwork for novel therapeutic options for advanced CCA. Particularly, the discovery of IDH mutations and FGFR2 fusions in IH-CCA is of significance as pharmacologic inhibitors have been developed and first studies investigating their anti-tumor efficacy have been initiated in CCA. Finally, several biomarker studies on biliary tract tumor samples have shown a high rate of PD-L1 expression in these tumors, providing a rationale to consider immunotherapy. First clinical trials are ongoing and response rates of 20% were reported in selected PDL-1 positive advanced patients with pembrolizumab [39]. Moreover, promising data exist for microsatellite-instability – high CCAs – which have a high rate of somatic mutation – with respect to progression-free survival in response to checkpoint inhibition [40].

Disclosure Statement

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