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Biliary tract carcinomas: From chemotherapy to targeted therapy

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Contents

Abstract

Biliary tract carcinomas (BTC) are a group of tumours arising from the epithelial cells of intra- and extra-hepatic biliaryducts and the gallbladder, characterised by a poor prognosis.

Surgery is the only curative procedure, but the risk of recurrence is high and furthermore, the majority of patients present with unresectable disease at the time of diagnosis. Systemic therapy is the mainstay of treatment for patients who present recurrent or metastatic disease. Progress has been made in the last decade to identify the most effective chemotherapy regimens, with the recent recommendation of the combination of gemcitabine–cisplatin as the standard schedule.

Comprehension of the molecular basis of cholangiocarcinogenesis and tumour progression has recently led to the experimentation of targeted therapies in patients with BTC, demonstrating promising results.

In this review we will discuss the clinical experience with systemic treatment for BTC, focusing on future directions with targeted therapies.

Keywords: Biliary tract carcinoma; Cholangiocarcinoma; Gallbladder carcinoma; Chemotherapy; Targeted therapy

1. Introduction

Biliary tract carcinomas are a group of tumours arising from the epithelial cells of intra- and extra-hepatic biliaryducts and the gallbladder. They can be divided in gallbladder carcinomas (GBC) and cholangiocarcinomas

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(CC). The latter includes extrahepatic cholangiocarcinomas (EHC), intrahepatic cholangiocarcinomas (IHC) and Klatskin tumour, a CC occurring at the junction of the right and left hepatic ducts.

Histologically, more than 90% of BTC are well-differentiated and fall into the category of mucin-producing adenocarcinomas; other types, such as squamous cell carcinoma and small cell carcinoma are less common.

Even though BTC is the 2nd second most common primary hepatic tumour, after hepatocellular carcinoma (HCC), it is still considered to be a rare disease in the Western world, with an incidence of 1–2 cases/100,000. On the contrary, these neoplasms are more common in Eastern countries and South America, with up to 96 cases/100,000 [1].

Prognosis for advanced BTC, which is defined as metastatic or surgically unresectable, is very poor, as median overall survival (OS) is generally less than 1 year following diagnosis [2].

In the majority of cases there is no familial predisposition or specific genetic mutation. Hereditary forms, especially for GBC, have been associated with specific syndromes, such as Gardner Syndrome, Hereditary non-polyposis colorectal cancer (HNPCC) and Neurofibromatosis.

However, a number of environmental and pathologic conditions have been identified as probable risk factors. Biliary diseases such as primary sclerosing cholangitis (PSC) [3], cirrhosis, hepato/chole/choledocholithiasis, chronic cholecystitis, chronic non-alcoholic liver disease, and Hepatic C Virus (HCV) infection can all promote neoplastic transformation [4]. In Eastern countries, infection by liver flukes, such as Clonorchis sinensis or Opistorchis viverrini, has proven to be the strongest risk factor.

CC is more common in the 7th decade, with a slight prevalence for men, whereas GBC tends to mainly affect women with a median age of onset at 65 years. This gender difference might be explained with the different prevalence of certain risk factors (e.g. cholelithiasis is more common in women).

2. Molecular, genetic and epigenetic events in BTC

BTC is the result of malignant transformation of cholangiocytes, in which genetic and epigenetic changes are required for transformation, promotion, and progression [5].

In this section we will illustrate the main molecular pathways that are related to cancerous transformation, such as NO, COX2 and EGFR. We also report the incidence of specific, key role gene mutations in BTC. Finally we provide an outlook on the newest perspectives in molecular research.

Fig. 1 summarises the most important molecular events involved in carcinogenesis. Chronic inflammation is the main risk factor that contributes to the pathogenesis of this kind of neoplasm, as it induces cholangiocytes to produce chemokines and cytokines. This signal cascade results in promotion of growth and survival advantages: the subsequent activation of nitric oxide (NO) or cyclooxygenase-2 (COX2) pathways causes damage in the DNA mismatch repair machinery. The resultant DNA damage leads to accumulation of mutations and alteration of genes involved in cell growth, inhibition of apoptosis and promotion of angiogenesis, such as K-RAS, p53, mdm2, waf-1, p16INK4a, DPC4/Smad4 and APC [6–13].

A close relationship exists between COX-2 and Epithelial Growth Factor Receptor (EGFR) family members. In mice models, constitutive expression of ErbB2 and EGFR in gallbladder and biliary tree epithelia results in elevated COX-2 and subsequent development of BTC. Activation of the EGFR pathway may occur via various different mechanisms. It has been demonstrated that TGF-α, commonly contained in bile acids stimulates the activation of EGFR and its downstream pathways [14,15]. These include, among others, enhancement of COX-2 expression and prostaglandin E2 (PGE2) production that, through the PGE2/EP1 receptor, induces transactivation of EGFR. This signalling is, in part, enhanced by Src [16], a tyrosine kinase (TK) implicated in tumour cell proliferation, adhesion and metastasis [17]. Src is also an important mediator of many downstream effects of EGFR [18].

The EGFR pathway regulates the synthesis and secretion of several angiogenic growth factors, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and Interleukine 8(IL-8) [19].

Acquired genetic mutations in the EGFR pathway may be responsible for the activation of carcinogenesis. EGFR-activating mutations in the TK domain are found in about 15% of cases [20,21], and EGFR gene amplifications are detected in 6% of BTC [22].

Other members of the EGFR family, such as ErbB2, may also be intricately involved; for example, overexpression of ErbB2 which is detected in hepatolithiasis and PCS [23,24], has been reported in EHC [25,26], IHC [27,28] and CC in general [29].

The mutational status of K-RAS has been evaluated in several clinical and preclinical studies that are summarised in Table 1. We recently demonstrated that the incidence of K-RAS mutations in Italian patients was low (6.1%) [25]: this is in accordance with other Western studies [30,31]. However, the highest percentage of K-RAS mutations was found in Eastern countries (38–52%) suggesting that geographical differences in aetiology or genetics might explain this variability [32–36].

B-RAF was found to be mutated in 22% of GBC and 33% of European IHC patients [37,38]. In our experience we observed B-RAF mutations in 8.1% of patients, which is generally lower than other reports [25].

Mutational analysis of PI3KCA revealed that hotspot mutations within exons 9 and 20 are rare in BTCs and the frequency ranges from 4% to 9%. Mutations in PTEN were only found in 4% of CC without loss of protein expression [25,39].

The aberrant expression of specific microRNAs (miRNAs), important mediators of posttranscriptional regulation