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Tumour Review

Targeting specific molecular pathways holds promise for advanced gallbladder cancer therapy

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ABSTRACT

Gallbladder cancer is the most common and aggressive malignancy of the biliary tract. The complete surgical resection is the only potentially curative approach in early stage; however, most cases are diagnosed in advanced stages and the response to traditional chemotherapy and radiotherapy is extremely limited, with modest impact in overall survival. The recent progress in understanding the molecular alterations of gallbladder cancer has shown great promise for the development of more effective treatment strategies. This has mainly resulted from the identification of molecular alterations in relevant intracellular signaling pathways—Hedgehog, PI3K/AKT/mTOR, Notch, ErbB, MAPK and angiogenesis—which are potential tailored targets for gallbladder cancer patients. This review discusses the recent remarkable progress in understanding the molecular alterations that represent novel prognosis molecular markers and therapeutic targets for gallbladder cancer, which will provide opportunities for research and for developing innovative strategies that may enhance the benefit of conventional chemotherapy, or eventually modify the fatal natural history of this orphan disease.

Introduction

Gallbladder cancer (GBC) is the most frequent type of biliary tract cancers (BTC) and the sixth most common gastrointestinal cancer worldwide, with an annual incidence of 2.2/100,000 and mortality rate of 1.7/100,000. Although this cancer is referred to as an orphan disease in the United States, GBC tumors affects many thousands of individuals worldwide, with the geographic areas with the highest mortality rates being Chile, Bolivia, Korea, Nepal, Bangladesh, Japan, Peru, Czech Republic and Slovakia [1]. Since the first description of the gallbladder carcinoma, studies have established a characteristic pattern of late diagnosis and ineffective treatment for this disease [2].

Considering there are currently few therapeutic options for patient with GBC, new therapeutic approaches must be explored in order to direct rational therapies to improve outcomes while minimizing secondary toxic effects. Therefore, a better understanding of the pathological molecular mechanisms of gallbladder carcinogenesis is essential for improving the diagnosis, prognosis, and for developing novel targeted therapies for patients with advanced GBC.

Studies available in the literature do not clearly define the molecular genetic mechanisms involved in the pathogenesis of GBC and also do not propose molecular classifications of advanced tumors for the development of drug tailored therapy. However, these are areas of intense active research and recently several pathways involved in advanced GBC have been proposed which could be candidates for small-drug inhibitors that avoid the secondary effects of cytotoxic therapy and improve the response of the recurrent and highly resistant tumor cells.

Pathological stage classification and management of gallbladder carcinoma

In as many as 50% of cases, GBC are incidentally discovered during pathological analysis after a simple cholecystectomy for gallstone disease. The most robust indicator of patient survival is the

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pathological stage. The 2012 AJCC staging atlas incorporates several changes from prior editions [3]. Specifically, cystic duct is now included in this classification. The N classification now distinguishes hilar nodes (N1: lymph nodes adjacent to the cystic duct, bile duct, hepatic artery, and portal vein) from other regional nodes (N2: celiac, periduodenal, and peripancreatic lymph nodes, and those along the superior mesenteric artery). In the stage grouping, locally unresectable T4 tumors are stage IV, while lymph node metastasis is classified as stage IIIB (N1) or stage IVB (N2). These changes have been better correlated with surgical resectability and patient outcome. [3]. Overall, 5-year survival rates are close to 90% for T1 tumors [4,5]. As regards mucosal tumors (T1a), any therapy beyond a cholecystectomy seems unnecessary except in those cases where the Rokistansky Aschoff sinuses are superficially compromised; even in the absence of evident infiltration of the surrounding tissues, these cases have a significantly worse prognosis similar to advanced tumors, suggesting that a second extended surgery is needed [6]. However, for those with muscular invasion (T1b), the controversy regarding the need for further treatment continues but gradually the opinion in favor of extended surgery has gained position among the surgeons [4]. Subserosal GBC (pT2) has better survival: the 5-year survival rate appears to be improved with more radical resection and depends on the primary tumor site location in the gallbladder wall, being 42.6% for tumors infiltrating the hepatic side versus 64.7% for tumors infiltrating the peritoneal side of the gallbladder [7]. Patients with lymph node metastases (Stage IIIB or higher) or locally advanced tumors (Stage IVA or higher) rarely experience long-term survival [3]. New morphological or molecular studies are required to define a subgroup of pT1b patients who require additional surgery. Subserosal GBC (pT2) has a better survival, with an extended cholecystectomy including a liver wedge resection and lymphadenectomy, following by adjuvant chemotherapy.

The only curative treatment for GBC is complete surgical resection, which is only possible in the very early stages of the disease. Even with complete surgical resection, which is possible only in a minority of patients, 50% will develop locoregional recurrence, and less than 10% of these patients will survive to 5 years. The most commonly used adjuvant treatment in patients with GBC is gemcitabine (GEM) or 5-fluorouracil (5-FU)-based chemotherapy, with or without radiotherapy [8]. There is a clear benefit to adjuvant treatment with GEM for pancreatic cancer, but the data for GBC is less robust [9].

Unfortunately, most patients are diagnosed in the advanced stages of the disease, when the standard treatment is palliative chemotherapy. There is little information regarding standard treatment for patients with advanced BTC (biliary tract cancer). Most studies have included patients with GBC and cholangiocarcinomas (CC), although these cancers are different in terms of etiologies, physiologies, and treatment responses. The most important study is the Advanced Biliary Cancer (ABC-02) trial that compared treatment with GEM and GEM + cisplatin (GEM/CIS) in patients with GBC ($n = 148$) or CC ($n = 262$) [10]. The combination arm improved overall survival (OS) from 8 months with GEM alone versus 11.7 months with GEM/CIS (hazard ratio (HR): 0.68, $p = 0.002$), without adding significant toxicity. Thus, this combination was established a new standard treatment for patients with advanced BTC. This observation was confirmed in a meta-analysis study [11].

Given this background, it is important to define a molecular classification that includes prognosis and predictive markers for patients with potentially resectable T2 subserosal tumors to allow us to discriminate high-risk patients and thus tailor the treatments. On the other hand, in T3 and T4 patients new molecular and signaling pathway characterizations are required to guide personalized treatment decisions in the future.

Pathogenesis and geographical variations of gallbladder cancer

The worldwide geographical variations in the incidence of gallbladder cancer and some interesting clinicomorphological features in different populations suggest that different carcinogenic pathways might be involved in gallbladder cancer histogenesis: (a) presence of gallstones or absence; (b) frequency of the adenoma-carcinoma sequence and (c) the anomalous pancreaticobiliary ductal junction (APBDJ).

Gallstones are the greatest risk factor for developing GBC and are present in between 60% and 90% of the cases [4], and in particular ethnicity plays an enormous role in its prevalence. American Indians of North, Central and South America, who have high prevalence of cholesterol gallstones disease, also have a high incidence of gallbladder carcinoma. By contrast, a low prevalence and marked differences in the type of stones have been reported in Asian populations [12,13]. Gallstones are strongly related with Amerindian genes and have been associated with an increase in bile acid synthesis, polymorphisms in the lipid metabolism, and a high rate of cholesterol lithogenesis [12]. The evidence shows that the chronic presence of gallstones produces a persistent inflammatory state strongly associated with the development of metaplasia and dysplasia and the accumulation of loss-of-heterozygosity (LOH) in various tumor suppressor genes [14–16]. Mutational profilings performed on GBC samples from several countries, including Italy, Hungary, China, the USA, Chile and Japan [17–21], have revealed homogeneity in genetic abnormalities among samples from different regions. The early molecular changes associated with gallstones and chronic cholecystitis in GBC consistently present TP53 mutations in around half of the cases, and a low frequency of mutations in KRAS and other genes similar to the pattern found in the chronic inflammation induced by endogenous carcinogens [16].

The incidence of adenomas and polypoid lesions/ intracholecystic papillary-tubular neoplasm (ICPN) [22] are different in Western and Asian populations and emphasizes the importance of ethnic background in the management of patients with gallbladder polyps [23]. These have been reported as an independent risk factor for developing gallbladder carcinoma in patients with an Indian background compared to Caucasian, Chilean patients (5.5% versus 0–1%, respectively) [24] and some genetic alterations also have a different frequency, for example the KRAS and P53 mutations are almost completely absent in carcinomas arising in adenomas [25,26].

A special case is the GBC related to the APBDJ, a rare congenital anomaly observed among the Japanese population and considered to be a risk factor in the Asian countries, with a occurrence rate of 3–18% for developing biliary tract carcinoma (including gallbladder cancer) and it is related to relatively young female patients without gallstones [27]. The reflux of pancreatic juice into the extrahepatic biliary duct and GB results in bile changes, inducing chronic inflammation and increased cellular proliferation, which leads to epithelial hyperplasia, metaplasia and biliary tract carcinoma. APBDJ-related GBC has a frequency of KRAS mutation of 50–83% [28] of cases, particularly in codon 12, compared with GBC cases unrelated to APBDJ [29,30], where KRAS mutation presents lower frequencies (2–29%) [31–33]. Interestingly, KRAS mutations are also observed in 25–31% of gallbladder adenomas compared with dysplasias and carcinomas, where KRAS mutations are rare [34,35]. The high frequency of mutations in the RAS pathway observed in gallbladder adenomas compared to gallbladder carcinomas suggests that the two lesions emerge from different molecular pathways. Fluke-related cholangiocarcinoma is an endemic disease in some regions of Asia, including Singapore. Interestingly, fluke-related cholangiocarcinoma has a genetic profile