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Review

Matching genomic molecular aberrations with molecular targeted agents: Are biliary tract cancers an ideal playground?

Loic Verlingue [a,b], Antoine Hollebecque [a,b], Valérie Boige [a], Michel Ducreux [a], David Malka [a,*,1], Charles Ferté [a,1]

[a] *Département de Médecine Oncologique, Gustave Roussy, Université Paris-Saclay, Villejuif, F-94805, France*
[b] *Département d'Innovation Thérapeutique et Essais Précoces, Gustave Roussy, Université Paris-Saclay, Villejuif, F-94805, France*

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Abstract Biliary tract cancers (BTCs) are a heterogeneous group of tumours with geographical discrepancies in terms of incidence and risk factors. However, a convergent genomic and epigenetic mutational landscape emerges from the genome-wide screens of BTCs in South East Asia, Latin America and in the Western World. Specificities are observed for some alterations and anatomical subtypes: frequent fibroblast growth factor receptor 2 (*FGFR2*) and isocitrate dehydrogenase 1/2 (*IDH1/2*) alterations are specific to intrahepatic cholangiocarcinomas (ICCs), whereas frequent *ERBB2* oncogene alterations are specific to extrahepatic cholangiocarcinomas (ECCs) and gallbladder carcinomas (GBCs). Until now, the outcome of patients with BTCs treated by molecular targeted agents (MTAs) alone or in combination with conventional chemotherapy in non-biology driven trials remains poor and does not exceed the outcome of patients treated with chemotherapy alone. Encouraging reports of biology-driven therapeutic approaches should accelerate the clinical development of MTAs in BTCs. Additionally, frequent epigenetic aberrations such as *IDH1/2* mutations and switch/sucrose non-fermenting (SWI/SNF) complex dysfunctions suggest that epidrugs must also be considered. In this review, we expose the rationale and feasibility to biologically drive the treatment of BTC patients.

* *Corresponding author*: Département de Médecine Oncologique, Gustave Roussy, 114 rue Edouard Vaillant, F-94805, Villejuif, France. Fax: +33 (0)1 42 11 52 29.
E-mail address: david.malka@gustaveroussy.fr (D. Malka).
[1] These authors have contributed equally to this work.

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1. Introduction

Biliary tract cancers (BTCs) are a heterogeneous group of neoplasms emerging from the bile ducts. Classically, BTCs include cholangiocarcinomas, which are divided into extrahepatic cholangiocarcinomas (ECCs) and intrahepatic cholangiocarcinomas (ICCs), separated by the second-order bile ducts, and gallbladder carcinomas (GBCs) (Fig. 1) [1]. A transitional type of hepatocellular-cholangiocellular carcinoma has also been described and represents approximately 1% of all liver cancers [2,3]. Within primary liver cancers, ICCs account for up to 15% of cases, and represent the second most frequent liver cancer after hepatocarcinomas [4–6]. The ICC incidence is increasing worldwide, while ECC incidence is rather decreasing [4,7–9].

ECCs are usually revealed by a painless cholestasis that requires – in unresectable cases – endoscopic retrograde cholangiography for sampling and biliary stenting [10]. Infectious cholangitis is relatively frequent throughout disease course, especially after bile duct instrumental procedures, along with progressive cachexia. By contrast, signs and symptoms at diagnosis of ICCs are often scarce, which explains a frequent delay to diagnosis. Consequently, curative-intent resection is possible in less than 30% of the cases, with a median postoperative survival that barely exceeds 3 years [1,11].

When curative-intent surgery cannot be performed, systemic chemotherapy is the only option, and gemcitabine-platinum doublets are the standard of care. In such cases, overall survival remains below 12 months (Fig. 2) [12–14]. The limited therapeutic options and the rising incidence of ICCs have recently resulted in a 40% increase of the worldwide specific mortality rate [5,15]. Together with the management of specific risk factors (for instance, primary sclerosing cholangitis),the only recourse is to strive towards a deeper understanding of

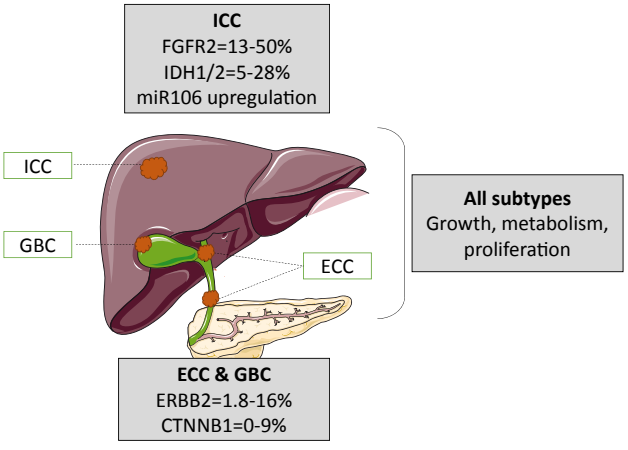

Fig. 1. The pathological subtypes of biliary tract cancers and their most frequent related molecular alterations (ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; GBC, gallbladder carcinoma).

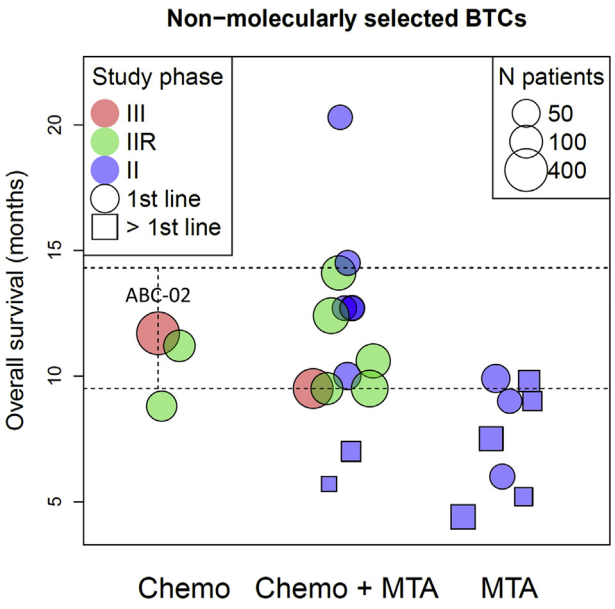

Fig. 2. Best median overall survival of biliary tract cancers (BTCs) patients treated in the first- and second-line setting (N, number; Chemo, chemotherapy; MTA, molecular targeted agent; R, randomised; dashed lines, confidence interval of the ABC-02 study).

BTC biology in order to widen the therapeutic options for patients.

Fortunately, a large amount of work has been recently accomplished to gain deeper insights in to the biology of BTCs. BTCs appear to be oncogene-addicted tumours, as most harbour well-characterised driver alterations that can be specifically targeted with molecular targeted agents (MTAs) – already available, or soon to be so, in the therapeutic armamentarium. Alongside with classical cancer pathways, numerous epigenetic modifiers (genes that encode for proteins implied in the epigenetic program of the cell) are found altered in BTCs. With such frequent and functionally important alterations, BTCs may be good candidates for personalised anticancer treatment, including MTAs and/or epidrugs (drugs that modulate the expression of epigenetic modifiers). We present here a rationale for treatment personalisation of BTCs.

2. Epidemiological, clinical and molecular features of BTCs

The incidence of BTCs is not random and very distinct risk factors are involved in different regions of the World. Intriguingly, a similar molecular pattern emerges across the continents, suggesting a robust role of somatic genetics and epigenetics on BTCs carcinogenesis.

In the United States of America (USA), ECCs and GBCs represent about 11,000 new cases per year and account for 3700 deaths [4]. Most patients diagnosed with a BTC in the Western World do not harbour