THE ITALIAN RARE BILIARY TRACT CANCER INITIATIVE (IRABICA)

A MULTICENTRIC OBSERVATIONAL STUDY OF GRUPPO ONCOLOGICO DELL'ITALIA MERIDIONALE (GOIM) IN COLLABORATION WITH GRUPPO ITALIANO COLANGIOCARCINOMA (GICO)

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Abstract

Introduction - About 90% of cholangiocarcinomas are adenocarcinomas with glandular or tubular structures lined by epithelial cells, with no bile production and with a variable degree of differentiation, arising in background of desmoplastic stroma. The remaining 10% is represented by rarer histological variants of which there is little knowledge regarding the biological behavior, molecular characterization, and sensitivity to the various possible therapies, including molecular-based treatments. Such rare tumors are described only in case reports or small retrospective series because of their exclusion from clinical trials. This national initiative, here presented, aims to address the following "unmet clinical needs" a) how much does histological diversity translate into clinical manifestation variety? b) are those chemotherapy regimens, recommended for conventional biliary tract cancers, potentially active in rare variants?

Therefore, epidemiological, pathological, and clinical characterization of series of rare biliary histotypes/variants, for which therapeutic and follow-up data are available, will be collected.

Methods - An Italian task force on rare tumors of the biliary tract (IRaBiCa) has been created, whose initiative is a multicenter retrospective study involving 34 Italian cancer centers.

Clinical data from approximately 100 patients will be collected and analyzed. Continuous variables will be presented as median ± standard deviation, while categorical variables will be expressed in terms of frequency. Kaplan-Maier analyses will be used to compare disease free, progression free and overall survival, according to the different histotypes.

Conclusions - We expect to gather novel data on rare histotypes of biliary tract cancer that will be useful to support their molecular and immunological characterization.

Keywords

Rare tumors, biliary tract cancer, rare histotypes;

Introduction

Cholangiocarcinoma (CCA) represent 3% of all gastrointestinal tumors[1]. In Italy, in 2020, 5,400 new diagnoses were reported (men = 2,400; women = 3,000)[2]. The incidence of intrahepatic cholangiocarcinoma is rising globally and this is not only due to an improvement in diagnosis[3]. According to 5th edition of World Health Organization (WHO) it is divided into the following types: a) intrahepatic cholangiocarcinoma (iCCA) when it is found proximal to the second order bile ducts; b) perihilar or Klatskin cholangiocarcinoma (pCCA) when located between the second order bile ducts and the origin of the cystic duct; c) distal cholangiocarcinoma (dCCA) when it arises between the origin of the cystic duct and the papilla of Vater (WHO 5th edition). About 90% of CCAs are adenocarcinomas with glandular or tubular structures lined by atypical epithelial cells, with no bile production and with a variable degree of differentiation, arising in a context of desmoplastic stroma. The remaining 10% is represented by rarer histological variants, starting with adenosquamous, clear cell, signet ring cell, lymphoepithelioma-like, and undifferentiated histological types (Table 1)[4].

Recently, the improvement of the knowledge in terms of molecular characterization of these malignances allowed the identification of new therapeutic options. In fact, most recent statistics suggest that 40-50% of patients with CCA have at least one genetic alteration that might be clinically actionable[5]. The frequency of these genetic alterations varies depending on whether we refer to the intrahepatic, extrahepatic and gallbladder forms. In particular, 75% of the identifiable genetic alterations are of intrahepatic relevance, above all fusions / rearrangements of *FGFR2* (10%), and mutations of *IDH1/2* (10-20%). *ERBB2/3* amplifications (10%) and *KRAS* mutations (8-45%) are more represented in the extrahepatic forms[6,7,8].

The first-line use of durvalumab in combination with chemotherapy is now clinical practice[9]. Recently, several molecularly targeted drugs have been approved by FDA such as pemigatinib[10] and futibatinib[11] in patients with fusion and/or rearrangement of FGFR2 and ivosidenib in patients with IDH1 mutations[12]. Additionally, drugs that have received agnostic approval should also be considered[13,14,15]. Indeed, several targeted molecules are currently being studied in phase II and III trials[16]. Nevertheless, no data are available on rare histotypes of CCA.

These histotypes differ in epidemiological, pathogenetic, molecular and clinical characteristics. The most frequent is the adenosquamous histology, with an incidence of 2-3% of CCA and 4-8.9% of gallbladder tumors. Sarcomatous histology (4-5% of iCCA), signet-ring cell histology (1.3%), and cholangiolocarcinoma

(0.6%-1%) follow in order of incidence. No data are available on the real incidence of histological types such as clear cell histology, mucoepidermoid and lymphoepithelioma-like histology. These rare variants also include a controversial entity, the combined hepatocholangiocarcinoma, which some authors considered as a poorly differentiated cholangiocarcinoma [WHO 5th ed.]

All the rare variants of cholangiocarcinoma also differ in terms of prognosis. Adenosquamous type presents a median overall survival (OS) of 6-20 months[17], while for the sarcomatoid histological type, data in the literature document a median OS of 3 months[18]. Instead, the lymphoepithelioma-like and the clear cell histotypes appear to have a less aggressive biological behavior and a better prognosis[19.]

Little is known about the pathogenesis of these neoplasms. Some hypotheses have been formulated. For example, two possible pathogenetic hypotheses have been formulated about the oncogenesis of signet ring cell carcinomas (SRCCs): 1. the presence of ectopic gastric mucosa from which the carcinomatous form then originates, 2. the evolution of SRCC from a gastric-type epithelial metaplasia, the latter often associated with the presence of duodenal ulcer and elevated intraluminal acidity[20]. Furthermore, a strong association between lymphoepithelioma-like type and Epstein-Barr-virus (EBV) infection has been demonstrated[21]. iCCA with ductal plate malformation arises in a healthy liver or with chronic liver disease such as Caroli's disease, fibropolycystic disease, von Meyenburg complex and congenital liver fibrosis. The latter are often associated with Malformation of the Ductal Plate (DPM), a structure found in the fetal liver that in the post-natal period is no longer physiologicallydetectable[22]. The national initiative here presented aims to address the following “unmet clinical needs” a) how much does histological diversity translate into clinical manifestation variety? b) do chemotherapy regimens recommended for common biliary tract cancers have clinical activity in these rare tumors?

Therefore, epidemiological, pathological and clinical characterization of series of rare histotypes for which therapeutic and follow-up data are available will be collected.

Methods

The IRaBiCa multicenter retrospective study of Gruppo Oncologico dell’Italia Meridionale (GOIM) in collaboration with Gruppo Italiano Colangiocarcinoma (GICO), aims to create a national task force to collect information regarding the epidemiologic, clinical, laboratory and possible risk factor characteristics of patients with rare histotypes of biliary tract epithelial tumors and, if available, information about treatments, follow-up and survival. Table 2 summarizes Italian centers involved in this study.

Study population

This retrospective multicenter study includes all patients with rare histotypes of biliary tract cancer currently on treatment and/or follow-up at the centers participating in the study. Inclusion and exclusion criteria are shown in table 3.

Data collection and study monitoring

Data from patients with rare histotypes of epithelial biliary tract cancer will be collected in a case report form (CRF) developed in Redcap. In the first part of the data collection form, information regarding the patient's medical history will be requested, this will be followed by a focus on the pathology staging at diagnosis, and finally information on the management of the disease in localized, advanced, and resectable stages will be requested.

CRFs will be compiled by accurately entering all available information requested.

Data collected and documentation acquired during the study will need to comply with the ALCOA + principles (attributable, legible, contemporaneously recorded, original or true copy, accurate, complete, coherence, enduring and available) to preserve data integrity. The lead principal investigator (PI) will be sent requests for missing data or clarification of inconsistencies or discrepancies. The study will be performed in accordance with the protocol and in adherence to the standards of good clinical practice (GCP). Adherence to the study protocol, the ethicality of the trial, and the integrity and validity of the data collected and entered into the data collection form are the responsibility of the principal investigator. Selected cases will be analyzed with DNA and RNA next-generation sequencing. The PI also warrants that the study will be performed in compliance with the patients' rights set forth in the Declaration of Helsinki (1964) and in accordance with EU Regulation 2016/679 on the protection of personal data. Any modification and/or implementation to the protocol will be submitted to the ethics committee according to current regulations.

Statistical analysis

All patients matching the inclusion and exclusion criteria, referring to the participating centers from January 1, 2002 to July 31, 2022, will be considered. Based on the data reported at the various centers, and in view of the low incidence of the rare epithelial variants of biliary tract carcinoma, it is expected that the sample size will be approximately 100 patients. Appropriate descriptive statistics indices will be used to summarize the characteristics of the patients and each histotype: continuous variables will be presented as mean ± standard deviation, while categorical variables will be expressed in terms of absolute frequency and

percentage. In order to analyze the possible associations between the categorical variables, contingency tables will be constructed and the Chi Square test will be estimated to assess the significancè of the association. For each histotype, the assessment of OS, disease free survival (DFS) and progression free survival (PFS) will be performed by Kaplan- Maier curve construction. Through the use of the Log-Rank test, statistical comparison will be made between the curves for subgroups of patients, identified according to histotype and chemotherapy treatment administered to the different groups of patients previously defined.
The multivariate proportional hazards model (Cox regression) will be used to identify predictors of cancer specific survival (CSS); in particular, the explanatory power of the histologic subtype and the treatment regimen used will be tested; the model will be adjusted for possible confounders such as sex, age, and possible comorbidities. P-values less than 0.05 will be considered statistically significant.

Conclusions

To the best of our knowledge, this is the first time that a large series of rare biliary tract cancers will be characterized based on a curated collection of clinical, pathological, and therapeutic data. These data should be useful to promote their molecular and immunological characterization and provide possible data for better therapeutic management.

Declaration of conflicting interest

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