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Research Article

Holistic Approaches in Oncotherapy

Retrospective Study of Cholangiocarcinomas Diagnosed in the Hospital of Fuenlabrada in the Period 2006-2016

Beatriz Losada Vila*, D Gutierrez, MV De Torres, I Juez, MC Pantin, J de la Rubia and JA Guerra

Medical Oncologist, Hospital Universitario de Fuenlabrada, Camino del Molino 2 – 28942 Fuenlabrada Madrid, Spain

***Corresponding Author:** Beatriz Losada Vila, Medical Oncologist, Hospital Universitario de Fuenlabrada, Camino del Molino 2 – 28942 Fuenlabrada Madrid, Spain.

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Abstract

Cholangiocarcinoma (CCA) is a rare cancer arising from the biliary tree with a poor prognosis and limited therapeutic options. Recent large characterisation studies have identified recurrent genetic alterations in CCA which can be targetable. In this study we explore clinical, analytic factors and also treatments received with the aim to differentiate prognosis and patterns of behaviour among them [1]

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Introduction

Biliary tract cancers is a group of malignancies that arise from the epithelial cells of the biliary tree. They are typically classified by anatomic origin site in intrahepatic and extrahepatic cholangiocarcinoma (IHCC, EHCC) and gallbladder cancer (GBC). Surgical resection remains the standard treatment for early stage disease. However, most of the patients are diagnosed in an advanced or metastatic disease, so palliative chemotherapy (gemcitabine and cisplatin) is the only option for them. Due to the paucity of effective treatments, cholangiocarcinomas have a bad prognosis. There is a tremendous need to better understand the disease biology, discover new therapies, and improve clinical outcomes for this challenging disease.

IHCC is the most common BTC and the second most common hepatic malignancy, accounting for 10–20% of all primary hepatic malignancies. Owing to the insidious nature of this group of cancers, they are usually diagnosed at an advanced stage and carry a dismal prognosis. Surgery is potentially curative in early stage disease. In cases of advanced and metastatic disease, the current standard of care is systemic chemotherapy with gemcitabine and cisplatin. Clinical response rates to these cytotoxic chemotherapies are low, with a 5-year survival of less than 10% for all three BTC subtypes. Nowadays we do not have clinical factors to predict survival and to select patients to receive a more aggressive treatment. [2-4]

Material and Methods

A retrospective descriptive study of all patients diagnosed with cholangiocarcinoma at the Universitary Hospital of Fuenlabrada in the period 2004-2016. Demographic data, hepatitis infection, location and treatment received (radiotherapy, surgery, chemotherapy) are included as variables. Variables are described by frequency distribution.

Results

36 patients diagnosed with cholangiocarcinoma during the 2006-2016 period. Median age 61 years [19-84]. Of these, 69.4% (25/36) men and 30.6% (11/36) women. 55.6% of the population were smoker (20/36) while 27.8% have an enolic habit. As for cardiovascular risk factors, Diabetes Mellitus and hypertension were found in 22.2% (8/36) and 52.8% (19/36) respectively.

Among the risk factors most related to the presence of tumors were: obesity, previous gallbladder infections, cirrhosis and viral hepatitis. Thus in our population, only 8.3% (3/36) is obese, 11.1% (4/36) developed a previous inflammation in the gallbladder (cholecystitis/cholangitis/biliary colic) requiring cholecystectomy. 2.8% were cirrhotic (1/36) for Hepatitis B, while another 2 patients (5.6%) presented Hepatitis C without liver cirrhosis.

13.9% also showed a thromboembolic event in the diagnosis or in the following months (portal thrombosis/pulmonary thromboembolism). 58.3% (21/36) were diagnosed with synchronous metastatic involvement whereas 41.6% (15/36) were localized. Only 11.1% had no lymph node involvement. 60% were cT2-T3-T4, while 27.8% were cTx. The metastatic localization in which they debuted with synchronous metastases was mainly in 2 organs (hepatic + peritoneal/pulmonary) in 47.6% (7/21), followed by single liver metastases (28.5% = 6/21), in 3 or more organs (pulmonary/peritoneal, ganglion/bone and hepatic) in 19.04% (4/21) and lymph nodes in 14.2% (3/21). Only in 4.8% (1/21) the involvement was isolated at the pulmonary level.

In those initially located, they progressed to the liver in 40% (4/10) of them, as a "tumor blast" (3 or more organs) in 30% (3/10), lymph node in 20% (2/10) and only peritoneal metastasis in 10% (1/10). No progression in 13.9% (5/36).

The initial tumor location was IHCC (63.9%) followed by EHCC (19.4%) and GBC (16.7%). A 38.9% required placement of biliary drainage prior to initiation of chemotherapy treatment. In the localized tumors, surgery followed by adjuvant chemotherapy is the standard of treatment. Gemcitabine was the most widely used in 80% (12/15), followed by Gemox and Cisplatin + Gemcitabine (because of quick progression, gemcitabine was started but cisplatin was added after seeing metastatic disease). The mean number of cycles received was 4, when the standard treatment is 6, having to be discontinued early due to hematologic toxicity and diarrhea in most patients [0-6]. Among the 15 patients, only 6/15 (40%) completed the 6 standard cycles. 2/15 (13.3%) patients did not receive adjuvant chemotherapy because of no lymph node involvement, while 7/15 (46.7%) also did not complete it.

In metastatic disease, only chemotherapy is allowed. Cisplatin + Gemcitabine was the preferred choice in 80% (16/20) followed by Gemcitabine (15%) and Gemcitabine + 5FU (5%). Just one patient (2.8%) did not receive chemotherapy treatment due to rapid progression and deterioration of the general condition.

58.3% were not subsidiaries of a second line of treatment. In case of receiving chemo, FOLFOX (19.4%) followed by 5FU/Capecitabine (8.3%), Cisplatin + Gemcitabine (2.8%), Irinotecan (2.8%), Gemox (2.8%) and Carboplatin + Taxol 2.8% patient with doubt of synchronous pulmonary carcinoma) were the preferred ones. As for the third line, only 16.7% of the population received it. The most widely used option were Taxanes (Docetaxel/Paclitaxel) in 11.1%, followed by 5FU/Xeloda (2.8%) and Irinotecan in another 2.8%.

Local hepatic treatment was only performed in 2 patients in whom the hepatic metastatic involvement was synchronous, operating at the same time as the primary tumor. 22.2% (8/36) received Radiotherapy (RT), with a palliative intention for bone metastases in 2/36 (5.5%). The remainder was curative: in 3/36 it was performed with neoadjuvant intention (1 died from surgical complications

and 2 others did not undergo surgery because large mass persisted, although it took 6 and 10 months to progress) and other 3/36 in adjuvant setting because of close margins (2/36 progress, 1/36 alive without disease).

Of the 21 patients who already had metastases at diagnosis, 90.5% (19/21) died of disease progression while 9.5% (2/21) are still alive with disease. Overall survival in patients with synchronous metastases is 13.8 months [1-89]. The time from tumor diagnosis to progression is 7.1 months [0-53].

Of the 15 patients who presented localized tumors, 66.7% (10/15) relapsed: 8 died and 2 alive with metastatic relapse. 1/15 patient died without disease, due to postoperative complications and only 26.6% (4/15) are free of disease at the present time. Of these 4 patients, follow-up is 5, 4, and 1 year, respectively.

The overall survival of patients with localized tumors is 24 months [6-112], with a time from tumor diagnosis to progression of 10.6 months [3-33]. If we analyze survival rates according to the location of the metastases, 27.7% (10/36) had exclusive hepatic involvement, being the survival in them of 6.5 months [1-20]. 13.8% (5/36) had only lymph node involvement with a median survival of 5.4 months [4-16]. The most common combined metastatic involvement is hepatic + peritoneal followed by hepatic + lymph node or hepatic + lung with a curiously superior survival of 26.5 months [5-89]. In them, a patient lives 89 months after a first hepatic surgery followed by HIPEC because of localized peritoneal progression.

Patients with 3 metastatic sites are usually liver, lymph node + peritoneal/pulmonary, with an overall survival of 24 months [2-112]. One patient lives 112 months receiving chemotherapy, liver resection in the beginning and nephrectomy (progression as renal metastases), dying after a few months with massive peritoneal carcinomatosis.

Among the patients who do not progress (4/36) we can not establish prognostic factors, given the short representativeness. In addition, the surveillance in 50% is less than 1 year (diagnoses at 2017). All of them are IHCC with a staging cT2-T3-T4N1, requiring biliary drainage in 50% and without other factors of interest except smoking and drinking habit in 50%. Analytically wide range of GOT from 18-476; GPT 28-588, CEA 2.3-18.1, Ca 19.9 4-29, decreasing at 6 months the Ca 19.9 value between 1-23.

Discussion

IHCC is a rare entity with a distinct clinical course and epidemiology from hilar and EHCC. IHCC makes up 8-10% of cholangiocarcinomas and 10-20% of all primary liver tumors. There remains a considerable amount of geographic variation in the incidence of IHCC worldwide; however, the overall incidence of this malignancy appears to be rising. Several risk factors have been identified, such as infectious causes (liver flukes, viral hepatitis), biliary tract disease [primary sclerosing cholangitis (PSC), hepaticolithiasis, biliary cystic diseases], metabolic syndrome, lifestyle choices (alcohol abuse, tobacco use), and cirrhosis. Despite this, a substantial number of IHCC patients do not have any identifiable risk factors, underlining the need for further work into the pathogenesis of this malignancy (5). In our population, 11.1% (4/36) developed a previous inflammation in the gallbladder, and less than 10% presented hepatitis B or C.

The efficacy of conventional palliative systemic chemotherapy (5-fluorouracil, mitomycin-C, and cisplatin) seems negligible. Gemcitabine is among several different new anticancer drugs under investigation in the treatment of advanced biliary tract cancer. Apart from its favorable toxicity profile, this novel nucleoside analog has shown activity in many solid tumors, including pancreatic adenocarcinoma. In view of the histogenetic affinity between the pancreas and the biliary tract, and several case reports describing the efficacy of gemcitabine in advanced gallbladder or cholangiocellular carcinoma, a number of phase II investigations have been undertaken. In the majority of these trials a conventional gemcitabine dose regimen of 1,000 to 1,200 mg/m on 3 consecutive weeks followed by a week of rest has been used.

In a total of seven studies involving 167 assessable patients, objective response rates up to 60% (36% in the largest trial composed of 39 evaluable patients), abrogation of progressive disease (complete response + partial response + stable disease) in 50% to 93%,

and overall survival times ranging from 6.3 to 16 months, have been reported. The consensus is that the tolerance of treatment was remarkable with only exceptional patients (< or = 5%) experiencing grade 4 hematologic toxicities. Nonhematologic side effects were infrequent and almost exclusively mild to moderate. In three of the trials, a formal clinical benefit analysis was included, suggesting that a considerable proportion of symptomatic patients will experience relief of tumor-related symptoms and/or weight gain. Possible options currently being investigated to further improve the therapeutic results of gemcitabine monotherapy include modifications of the dose regimen as well as combinations with other potentially synergistic anticancer drugs (plus cisplatin, oxaliplatin, docetaxel, mitomycin-C, and 5-fluorouracil/leucovorin). Objective response rates as high as 53% (for gemcitabine/cisplatin), and median survival times > or = 11 months with only a slight increase in frequency and severity of side effects have been reported (6). As we see in our study, Gemcitabine and Gemcitabine+ Cisplatin is the most widely used chemo, although not all the patients can complete it. Our overall survival is also similar to these trials.

However, not just chemotherapy has to be the unique treatment in them. The incidence and cancer-related mortality of IHCC continue to increase worldwide. At present, hepatectomy is still the most effective treatment for ICC patients to achieve long-term survival, although its overall efficacy may not be as good as that for patients with hepatocellular carcinoma (HCC) due to the unique pathogenesis and clinical-pathological profiles of IHCC. Surgical treatment includes R0 resection, lymphadenectomy, total gross resection of the involved biliary tracts, blood vessels and surrounding tissues in adjacent organs, and reconstruction. Postoperative adjuvant therapy and local-regional therapy after recurrence may improve survival. Liver transplantation (LT) is reported to have a moderate treatment effect on early IHCC although its efficacy remains controversial. Recent articles explain that we have to individualise these patients because in case of presenting isolated liver metastases can benefit of liver metastesectomy [7]. As we also see in our population, liver progression is the most common and those who have performed liver surgery have an improvement in overall survival. However, as we only have a few patients and we can not conclude anything nowadays.

Conclusions

Adjuvant chemotherapy (Gemcitabine) was not completed in almost 50% of the population, with a relapse of 80% of patients with localized tumors. The time from diagnosis of tumor to progression is 10.6 months.

1. The most used chemotherapy in metastatic disease is Gemcitabine + Cisplatin followed by FOLFOX for second line. Time from diagnosis of the tumor to progression is 7.1 months. Second and third line of chemotherapy patient subsidiaries are in 58.3% and 16.7%, respectively.
2. Surgery can be an option in patients with isolated metastatic disease (2 cases achieve long survival with HIPEC, nephrectomy and liver surgery up to 112 months).
3. Hepatic involvement is the most frequent metastatic site in both patients with synchronous metastases and patients with localized tumors who relapse.
4. Neoadjuvant chemoradiotherapy is not common in our population. In 2/3 of the patients who completed it, tumor can not be resected by persistence but achieves a median time to progression of 10 months. RT is a palliative option used in those with bone involvement and pain.
5. 4/36 patients are still alive without disease, without being able to identify a common predisposing factor in them except the intrahepatic location.
6. We need to establish predictive factors of response in this profile of patients to select those in which we must be more aggressive with the treatment or not.

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