Biliary Tract Cancers

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1. Introduction

Biliary tract carcinomas (BTCs) are a heterogeneous group of malignancies arising from the epithelial lining of the bile ducts or gallbladder [1][2]. While relatively uncommon in the United States, approximately 23,000 new cases diagnosed annually, the incidence of BTCs has been increasing [3][4][5]. Cholangiocarcinoma alone represents an estimated 3% of all gastrointestinal malignancies and is the second most common primary hepatic malignancy after hepatocellular carcinoma [5].

When diagnosing BTC, it is important to distinguish between intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcnoma (eCCA), gallbladder cancer (GBC), and ampulla of Vater carcinoma (AVC) as each sub-type has its own specific characteristics and variations in tumor biology [2]. Pathologic diagnosis is essential prior to any non-surgical treatment, but biopsies are often technically difficult or result in inadequate tissue sampling [6]. ERCP-guided biopsies are preferred, but EUS-guided fine needle aspiration may be considered if ERCP is unsuccessful. However, liquid biopsy utilizing ctDNA or cfDNA is gaining much attention as it may overcome many of the challenges inherent in diagnosing BTC [7].

Prognosis is typically dismal for patients with BTC. Five-year survival rates are currently less than 5% for unresectable and less than 40% for resectable tumors [1][8]. As BTCs are generally asymptomatic in early stages, 60–85% of patients present with metastatic or unresectable disease [6][8]. Even in the 30–40% of patients with resectable disease who undergo potentially curative surgery, approximately 50% develop recurrent disease [9][10][11]. Although 5-year overall survival (OS) following curative surgical resection differs based on anatomic site, for patients with cholangiocarcinoma (CCA), it is estimated to be 40% in radical (R0) resection but falls to 20% in cases with nodal and vascular involvement [11].

Systemic chemotherapy is the standard treatment for advanced BTC and can currently lead to a median OS of approximately 12 months [6]. Immunotherapy and targeted therapies are also emerging as a promising treatment options for advanced BTC. A number of actionable alterations have been or are currently under investigation in clinical trials in both the front-line and chemotherapy-refractory setting [6][12].

2. Local and Systemic Consequences of Advanced Disease

Patients with BTC often experience symptoms from both systemic and local consequences of disease. Frequently reported symptoms include jaundice, abdominal pain, pruritus, nausea, unintentional weight loss, fever, and fatigue [13][14][15]. In addition to directly impacting QoL, these symptoms have also been found to adversely impact emotional well-being, as well as physical and cognitive functioning [16][17]. Early and effective symptom management has the potential to improve quality of life, as well as mortality, for many patients.

Patients with advanced BTC have a particularly high chance of developing obstructive complications. Gastric outlet obstruction may be amenable to endoscopic duodenal stent placement. As patients often can only consume clear or full liquid diet post-procedure, duodenal stent placement may be a better option for palliation in patients with poor performance status, significant comorbidities and/or limited life expectancy [18][19]. Pancreatic duct obstruction may lead to exocrine pancreatic insufficiency, which can be managed with pancreatic enzyme replacement therapy [19].

Over 90% of patients with extrahepatic biliary cancer present with jaundice due to biliary obstruction [13]. Although a less common presenting symptom, acute cholangitis due to malignant biliary obstruction can be life-threatening. Adequate biliary drainage is critical not only in managing acute cholangitis and symptoms related to jaundice, such as pruritis, anorexia, and sleep disturbances, but also in enabling palliative systemic treatment. ERCP-guided biliary stent placement is the preferred strategy for palliating malignant biliary obstruction, especially in patients with poor performance status. However, percutaneous biliary draining may be pursued in patients where ERCP has been unsuccessful [20].

Although ERCP is generally felt to be a safe procedure, there are several serious complications to be aware of including acute cholangitis. In one retrospective review, more than 20% of patients with malignant hilar biliary obstruction experienced post-ERCP cholangitis [21]. Higher rates of post-ERCP cholangitis in patients with malignant hilar biliary obstruction are likely due to difficulties in achieving complete drainage in this population [21][22]. Stent type has also been identified as a possible risk factor for post-ERCP cholangitis. Several prospective and retrospective studies comparing metal with plastic stents found numerically lower rates of post-ERCP cholangitis with metal stents [21][23][24]. It should be noted that plastic biliary stents require replacement approximately every 3 months due to relatively high occlusion rate. Consequently, metallic biliary stents, which remain patent on average 7 months, may be preferred in many patients with advanced BTC [18][20].

3. Systemic Chemotherapy: Adverse Effects and Impact on Quality of Life

Chemotherapy may relieve tumor-related symptoms, improve quality of life, and prolong survival in select patients with advanced BTC [25]. In others, particularly patients with already poor performance status or very advanced disease, systemic chemotherapy can lead to a rapid decline in HRQoL [17][26]. A clear understanding of how systemic chemotherapy impacts quality of life is vital in determining which patients benefit from treatment and in navigating treatment discussions.

The phase III ABC-02 trial established the combination of gemcitabine and cisplatin as the standard of care first-line treatment for patients with advanced BTC [27]. Eligible patients with nonresectable, recurrent or metastatic BTC (iCCA, eCCA, GBC, or AVC) were randomly assigned to receive gemcitabine plus cisplatin or gemcitabine alone for up to 24 weeks. Randomization was stratified by primary tumor site, extent of disease, recruiting center, previous therapy, and performance status. Of the total 410 patients enrolled, 58.7% were reported to have a primary tumor arising from the bile duct. The median survival was statistically longer at 11.7 months in the gemcitabine plus cisplatin group compared to 8.1 months in the gemcitabine group ($p < 0.001$). These results were then supported by the Japanese phase II BT22 study which also compared this combination to gemcitabine alone in patients with locally advanced or metastatic BTC [28].

The combination of gemcitabine plus cisplatin has a favorable toxicity profile even when compared to gemcitabine. ABC-02 reported similar frequencies of grade 3 or 4 adverse effects between gemcitabine plus cisplatin (70.7%) and gemcitabine alone (68.8%) [27]. The number of patients who discontinued treatment due to toxicity was also similar between gemcitabine plus cisplatin and gemcitabine groups (10.4% versus 8.6%). Notable grade 3 or 4 toxic effects of gemcitabine plus cisplatin included neutropenia (25.3%), anemia (7.6%), thrombocytopenia (8.6%), fatigue (18.7%), nausea (4.0%), and vomiting (5.1%). Grade 3 or 4 abnormal liver function was also seen but was higher in the gemcitabine alone group (27.1% versus 16.7%), likely due to poorer local disease control.

BT22 reported a similar toxicity profile with the most common grade 3 or 4 adverse events being neutropenia (56.1%), thrombocytopenia (39.0%), and anemia (36.6%) [28]. Common adverse events of any grade included anorexia (80.5%), nausea (68.3%), fatigue (58.5%), vomiting (48.8%), constipation (36.6%), and diarrhea (31.7%). Within the gemcitabine plus cisplatin arm, a total of 17% of patients discontinued treatment due to adverse events, and 9.7% of patients required dose adjustments.

Rates of treatment compliance and adverse events reported in clinical trials do not necessarily translate into how patients tolerate treatment in practice. To this end, the long-term outcomes and quality of life data of patients enrolled in ABC-02 was published in 2016 [29]. A total of 324 patients consented to completing the EORTC QLQ-C30 HRQoL questionnaire, with only 268 (83%) patients returning at least one form. Treatment mean differences in the HRQoL at 12 weeks between combination therapy and gemcitabine was not statistically significant for the majority of scales assessed. After controlling for patient characteristics and baseline HRQoL, only digestive symptoms and appetite loss were statistically significant at the 1% level, both in favor of gemcitabine plus cisplatin. While 59% of the data collected was missing at 12 weeks due to patient illness or death, the data is suggestive that HRQoL was not adversely affected.

Other gemcitabine-based or fluoropyrimidine-based regimens have demonstrated activity in clinical trials and are felt to be appropriate alternatives in the first line setting to gemcitabine plus cisplatin [30][31][32]. In select cases of locally advanced, unresectable BTC, particularly CCA, chemoradiation may also be considered as it can provide local symptom control an may potentially prolong OS [33]. Meta-analysis of BT22 and ABC-02 found patients with poorer performance status, ECOG 2, appeared to derive the least benefit from combination chemotherapy [32]. Therefore, in the absence of studies specifically for patients with poorer performance status, these findings suggest that monotherapy should be preferred in this population if chemotherapy is being considered at all and highlight the importance of early discussions focused on goals of care.

Due to the aggressive behavior of BTC and rapid decline of HRQoL associated with very advanced disease, further chemotherapy after failure of first line treatment is often challenging and/or contraindicated. Recently, the phase III ABC-06 trial determined the addition of FOLFOX to active symptom control (ACS) improved median OS in patients with advanced BTC (iCCA, eCCA, GBC, or AVC) after progression on gemcitabine and cisplatin compared to ASC alone (6.2 months versus 5.3 months) [34]. With regard to primary tumor site, iCCA was the most common site reported (44.4%), followed by eCCA (27.8%) and GBC (21.0%). Notably, patients enrolled in ABC-06 were particularly good candidates for further chemotherapy as eligibility criteria included an ECOG performance status of 0-1 and a life expectancy greater than 3 months. With regard to toxicity, grade 3 to 5 adverse events were reported in 69% of patients in the ASC plus FOLFOX group compared to 52% in the ASC alone group. The most commonly reported grade 3 to 5 chemotherapy-related adverse events were neutropenia (12%), fatigue or lethargy (11%), and infection (10%). The ASC plus FOLFOX group also experienced high frequency of grade 1 or 2 neuropathy (64%), nausea (37%), oral mucositis (35%), anorexia (31%), diarrhea (27%), thrombocytopenia (22%), and dysgeusia (20%).

Similarly, the phase IIB NIFTY trial presented at the American Society of Clinical Oncology (ASCO) 2021 found the addition of liposomal irinotecan (nal-IRI) to fluorouracil (5-FU)/leucovorin (LV) improved progression free survival (PFS) and OS compared to 5-FU/LV alone in patients with metastatic BTC after progression on gemcitabine plus cisplatin [35]. Patients with histologically or cytologically confirmed iCCA, eCCA, or GBC were enrolled and stratified by tumor site, as well as previous curative-intent surgery, prior to randomization. Patients with iCCA made up 42.5% of the study population. Ultimately, the median PFS was 7.1 months compared to 1.4 months, and the median OS was 8.6 months compared to 5.5 months, for nal-IRI plus 5-FU/LV and 5-FU/LV, respectively. The study was conducted in Korea only; otherwise, the eligibility criteria selected for a population similar to ABC-06 as ECOG 0-1 was required. Grade 3 to 5 adverse events were reported in 77.3% of patients in the nal-IRI plus 5-FU/LV arm compared to 31.4% of patients in the 5-FU/LV arm. The nal-IRI plus 5-FU/LV group experienced higher frequency of neutropenia (33.0%), fatigue (30.7%), constipation (29.5%), diminished appetite (27.3%), and nausea (25.0%) of any grade.

As the median OS benefit seen in both ABC-06 and NIFTY is modest, HRQoL data is pivotal to evaluate the true benefit. Quality of life and health status questionnaires, including EORTC QLQ-C30, EORTC QLQ-BILI, and EQ-5D, were collected in ABC-06, but the results have yet to be reported [34]. EORTC QLQ-C30 was also collected in the NIFTY trial over the course of 8 cycles of treatment [35]. Presented quality of life data from NIFTY is suggestive that there is no significant difference in HRQoL between patients treated with nal-IRI plus 5-FU/LV compared to 5-FU/LV alone.

Chemotherapy-induced peripheral neuropathy (CIPN) is often a major concern for both clinicians and patients as it has the potential to significantly impact HRQoL. While platinum agents are frequently associated with CIPN, the incidence and severity of CIPN varies depending on the choice of chemotherapy agent, dose, and duration of treatment. Notably, the reported incidence of grade 3 or greater CIPN in clinical trials utilizing platinum agents in treating advanced BTC are low [27][28][30][34]. Regardless, clinicians are advised to assess for neuropathy throughout the course of treatment and consider dose delays, dose reductions or discontinuation in those patients who develop intolerable symptoms or functional impairment [36]. To date, duloxetine is the sole agent with convincing data supporting its use in existing CIPN [37][38]. However, there is great interest in identifying new preventative and treatment strategies for CIPN.

Prognostic factors can play a vital role in identifying patients who would benefit from chemotherapy to prolong survival, alleviate tumor-related symptoms, and improve quality of life. ECOG performance status, disease status, number of metastatic sites, including presence of liver metastasis, gender, bilirubin, white blood cell count, neutrophil count, neutrophil-lymphocyte ratio, and hemoglobin level, have been identified as possible independent prognostic factors for BTC patients treated with chemotherapy [39][40][41][42]. Unfortunately, to date, these factors have limited accuracy in determining clinical outcomes.

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