REVIEW

Aging and biliary tract cancers: Epidemiology, molecular biology, and clinical practice

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Abstract: Biliary tract cancer (BTC) that contains cholangiocarcinoma, gallbladder cancer, and ampullary cancer is highly malignant and mostly diagnosed in elderly patients. Over the past decades, human life has globally risen; thus, aging emerges as the primary risk factor for BTC. However, an effective treatment for this vulnerable population remains a large clinical challenge. As a result, the incidence and mortality of TBC remains high. Here, we discuss the potential link between aging and BTC from the aspects of molecular and cellular mechanisms, surgical resection, and chemotherapy. In addition, we update a number of clinical trials that are currently ongoing in elderly patients. The overview of BTC in elderly patients is expected to help develop a new therapeutic strategy tailored to this elderly population, ultimately improving their life quality.

KEYWORDS
aging, biliary tract cancer, microenvironment, senescence, therapy

1 | INTRODUCTION

Biliary tract cancer (BTC) originally derived from the bile ducts is composed of cholangiocarcinoma, gallbladder cancer, and ampullary cancer.1,2 Even though BTC is a relatively rare tumor in adults that accounts for 3% of all gastrointestinal neoplasms, it is the sixth leading cause of cancer-related death worldwide and 5-year survival of BTC is 5%–15%, demonstrating the poor prognosis.3 Of note, more than 45% of BTC cases are diagnosed in patients with age over 80 years old.4 While treatment means of BTC are limited, surgical resection is at present considered as the only effective regimen. However, given the fact that the typical symptoms of BTC are lacking at
the early stages, the majority of patients are usually diagnosed at advanced stages that have missed the opportunity of radical surgical treatment. Thus, alternative therapeutic strategies are subsequently taken into account in these patients, including chemotherapy, radiotherapy, specific molecule-targeted therapy, and immune therapy. To date, the combination therapy with cisplatin (CDDP) and gemcitabine (Gem) is typically engaged to treat patients as the first-line chemotherapy or adjuvant chemotherapy following surgery.

Intrahepatic cholangiocarcinoma (iCCA) is the most common subtype of BTC with an incidence rate of 1.49 per 100,000 persons and accounted for 20% of liver-related deaths. Though most of iCCA are derived from biliary epithelial cells (BECs), iCCA can arise from a setting of viral hepatitis. Likewise, experimental iCCA can be also derived from hepatocytes, particularly under the influence of Notch overexpression. DDC-induced injury makes the oncogenically primed hepatocytes be reprogrammed to a cholangiocyte phenotype. Both iCCA and extrahepatic cholangiocarcinoma exhibit higher incidence in non-Hispanic Asian/Pacific Islander populations than non-Hispanic White people. It is emerging that in BTC, disease incidence and mortality are higher in patients with age of 80 or older than young population with age of less than 50.

Of note, the human life has dramatically increased over the past decades and simultaneously, the incidence of a variety of diseases associated with aging also has emerged as the large challenge, including cancer, Alzheimer’s disease, and other disorders. The world population over 60 years old is expected to be approximately 1.2 billion with 12% of the general population in 2025 and will reach to 2 billion with 22% of the population by the middle of this century. Accordingly, the incidence and mortality of BTC have been reported to increase annually. Indeed, a number of pathological events or factors due to aging have been identified to be associated with the development of BTC. For example, cellular oxidative stress, mitochondrial dysfunction, and DNA damage during the aging process were documented to mediate the tumorigenesis of BTC. In addition, accumulated senescent cells gave rise to a senescence-associated secretory phenotype (SASP) over the years, thus creating a dysfunctional environment that facilitates tumor development. Finally, senior patients mostly have experienced a progressive decay of immune systems, resulting in defects of antitumor immunity.

In this review, we primarily focus on discussion of the potential role of the aging in the development and therapeutic intervention of BTC, including current clinical trials of chemotherapy and targeted therapy in elderly patients with BTC.

2 MOLECULAR MECHANISMS UNDERLYING AGING-MEDIATED BTC

Aging is a biological and physiologic multistep event associated with cell development, but aberrant aging process such as rapid and sustaining aging process can alter cellular function, becoming a major risk factor for BTC. Growing research evidence has revealed that varied molecular mechanisms regulating aging process contribute to BTC initiation and progression. These typical cellular and molecular mechanisms include DNA damage, cellular senescence, and aging microenvironment changes.

2.1 DNA damage

DNA damage refers to DNA structural disruption in the cells, which involves oxidation of purines and pyrimidines, DNA single-strand breaks (SSBs), double-strand breaks (DSBs), bulky adducts, base alkylation, base mismatches, insertions, and deletions. A numerous factors can induce DNA damage, in which endogenous cellular sources contain mitochondrial oxidative phosphorylation, lipid peroxidation chain reactions, Fenton reaction, and Haber–Weiss reaction, while exogenous cellular inducers are UV radiation, pathogens, chemicals, pollutants, inflammation, foods, smoking, and others. Most of these factors induce DNA damage via a common pathway of increased reactive oxygen species (ROS) levels and products of the oxidative stress. When cells undergo DNA damage, cellular repairing systems are simultaneously activated in order to rescue the DNA dysfunction. Loss of this balance between DNA damage and repairing responses leads to cellular function impaired. DNA damage repair (DDR) is a multicomplex network event involving multiple signaling pathways, and the decreased level of DDR has been identified in different cancers. In BTC, up to 25% cases were found to have DDR defects. In the DDR network, ataxia-telangiectasia-mutated (ATM) and ataxia-telangiectasia-Rad3-related (ATR) enzymes, the essential non-redundant DNA damage sensors, play critical roles in the DSBs, SSBs, and DNA repair. ATM is generally recruited after DSBs occur, while ATR recognizes the regions of replication protein A-coated single-strand DNA to maintain genomic integrity in S or G2/M phase of the cell cycle. Both ATM and ATR trigger DNA damage mediators to participate in DNA repairing. ATR and ATM can activate checkpoint kinases (CHK) 1 and 2, respectively, which stimulate a downstream factor p53, committing to cell apoptosis and/or cell cycle arrest. At the same time, ATR and ATM activate breast cancer gene 1 (BRCA1) that renders cells sensitive.
to DNA repairing.\textsuperscript{28} Thereof, DDR functions to protect cells from DNA damage-mediated genetic instability.

Compelling evidence reported that several DDR gene mutations were found in about 20\% of BTC patients, including \textit{ATM}, \textit{TP53}, \textit{KMT2C}, \textit{ATR}, \textit{BRCA1}, \textit{MSH6}, \textit{MLHI}, and \textit{MSH2}.\textsuperscript{29} \textit{ATM} mutations with decreased kinase activity were observed in 6.7\% of BTC cases\textsuperscript{30} and \textit{TP53} mutation was reported in 33.9\% of BTC cases.\textsuperscript{29} Our group previously demonstrated that \textit{TP53} was frequently mutated in gallbladder cancer\textsuperscript{31,32} and neuroendocrine carcinoma of the gallbladder.\textsuperscript{33} In addition, Poly (ADP-ribose) monosaccharide (PARP) inhibitors were engaged to induce DDR pathways and suppress BRCA1/2-deficient tumors in breast cancer,\textsuperscript{34} lung cancer,\textsuperscript{35} and pancreatic cancer.\textsuperscript{36} Wang et al. found that cholangiocarcinomas with \textit{isocitrate dehydrogenase (IDH)} mutation displayed elevated DNA damage due to decreased DNA repair and thus they developed combined treatment strategies with PARP inhibition and radiation that enhance the effects on DNA damage and repair.\textsuperscript{37} Pan et al. demonstrated that ATM inhibitor AZD0156 blocked tumor growth in Gem-resistant and DNA polymerase θ-deficient BTC cells that lack the ability to repair DNA damage.\textsuperscript{38} Likewise, the combination treatment of ATR inhibitor AZD6738 and cytotoxic chemotherapeutic agent cisplatin inhibited G2/M arrest in p53-mutated BTC cell lines through increasing γH2AX, a marker of DNA damage.\textsuperscript{39} Thus, targeting mutated mediators in the DDR pathways may offer the novel therapeutic options for BTC therapy.

\subsection*{2.2 Cellular senescence}

Cellular senescence is defined as permanent growth arrest and is also observed during early developmental phases. A number of intracellular and extracellular factors can induce senescence, including oncogenic mutations, genomic instability, protein aggregations, oxidative stress, and telomere shortening.\textsuperscript{40,41} Mechanistically, these events trigger some genes to undergo cellular senescence.\textsuperscript{42} For instance, \textit{senescence-associated beta-galactosidase (SA-β-gal)} is the most widely used gene to evaluate senescent cells, as increased level of SA-β-gal is associated with glucose metabolism in cellular senescence.\textsuperscript{43} p16\textsuperscript{INK4a}, a part of the CDKN2a or INK4a/ARF locus, mediates cellular senescence and immunostaining of p16\textsuperscript{INK4a} is also frequently employed to detect senescent cells in vivo.\textsuperscript{44} Sasaki et al. reported the elevated expression of SA-β-gal, p16\textsuperscript{INK4a}, and p21\textsuperscript{WAF1/Cip1} by small bile ducts in primary biliary cirrhosis (PBC).\textsuperscript{45} Polycomb group protein Bmi1 expression was negatively correlated with the expression of p16\textsuperscript{INK4a} in cultured BECs, thus also serving as the senescent cell marker.\textsuperscript{46} Overexpression of EZH2 reduced p16\textsuperscript{INK4a} expression that is increased in senescent gall-bladder epithelial cells,\textsuperscript{47} pointing to EZH2 as a safe guarding factor against gallbladder mucosa senescence. Pro-inflammatory cytokines such as interferon gamma (IFN-γ), IFN-β, and tumor necrosis factor (TNF)-α showed the ability to induce activation of ATM/p53/p21\textsuperscript{WAF1/Cip1}, leading to cellular senescence of BECs.\textsuperscript{48}

Cellular senescence has a capability of modulating the cellular microenvironment to maintain local homeostasis.\textsuperscript{49} Cellular senescence also plays roles in the tissue microenvironment, contributing to the neoplastic-prone tissue landscape of old age.\textsuperscript{50} Elevated levels of SASPs can recruit immune cells to promote cell senescence via cell cycle arrest during wound healing, tissue remodeling, and tumor development.\textsuperscript{31} However, unexpected accumulation of senescent cells with aging can be detrimental to tissue homeostasis and impairs tissue regeneration, facilitating tumorigenesis.\textsuperscript{52} There are about 75 secreted components of SASP, including intercellular-cytokine (IL-1α), IL-6, IL-8, IFN-γ, vascular endothelial growth factor, matrix metalloproteinase 1 (MMP1), MMP3, and MMP10,\textsuperscript{53,54} most of which largely mediate tumor angiogenesis and tumor development.\textsuperscript{55} Accumulating evidence has shown that BECs express a number of pro-inflammatory cytokines and chemokines (e.g., IL-1, IL-6, IL-8, CX3CL1, and CCL2) before cancer occurs, thus establishing the inflammatory microenvironment favorable for the pre-carcinogenic event.\textsuperscript{42,56,57}

\subsection*{2.3 Aging microenvironment}

Tumor progression is largely dependent on the interactions between cancer cells and noncancerous components in the tumor microenvironment (TME). Aging can dramatically alter the TME to promote tumor progression and metastasis in BTC. Using mosaic mouse models, Seehawer et al. demonstrated that a necroptosis-associated hepatic cytokine microenvironment switched HCC to ICC development, in which Tbx3 and Prdm5 acted as major microenvironment-dependent and epigenetically regulated lineage-commitment factors to drive the transition from HCC to ICC.\textsuperscript{58} TME in BTC harbors stromal (e.g., fibroblasts, cancer-associated fibroblasts [CAFs], endothelial cells) and immune cells (e.g., infiltrating immune cells, tumor-associated macrophages [TAMs]). Although multiple cells of TME are suggested to undergo physiologically senescent process in the metastasis of BTC, robust evidence of molecular link between the altered cellular senescence and tumorigenesis is lacking. Thus, considerable effort should be added to decipher the molecular and cellular mechanisms in aging-mediated cancer progression.
Fibroblasts, which contribute to the primary production of the extracellular matrix, are the most common stromal component. In the aging microenvironment, SASP-associated fibroblasts undergo dramatic metabolic changes through the secretion of soluble factors, including cytokines, chemokines, and growth factors. In cancer, CAFs, known as α-smooth muscle actin (α-SMA)-expressing activated myofibroblasts, promoted growth and metastasis of iCCA. The increased CAFs were correlated with poor patient outcomes. Moreover, inhibition of α-SMA+ CAFs by nintedanib suppressed tumor growth in an iCCA animal model.

Macrophages are innate immune cells differentiated from circular monocytes in the blood. TAMs are tumor infiltrating macrophages that participate in remodeling of the TME and promote tumor progression. Targeting TAMs decreased tumor-initiating cells and attenuated infiltration of immunosuppressive cells such as regulatory T cells, restricting the growth of iCCA. TAMs increased expression of TNF-α and IL-6 that induce epithelial–mesenchymal transition and promote malignant transformation of cholangiocarcinoma. Blockade of TAM disrupted WNT signaling, thus suppressing cholangiocarcinoma progression. Hepatic macrophages known as Kupffer cells (KCs) augmented the release of TNF-α that activates JNK signaling in tumor cells to impair mitochondrial function and induce ROS, driving cholangiocellular tumorigenesis. In clinic, recent studies demonstrated that cholangiocarcinoma patients with the increased levels of CD86+/CD206+ TAMs exhibited poor survival.

Myeloid-derived suppressor cells (MDSCs) that are stemmed from the bone marrow are immunosuppressive cells including neutrophils and monocytes. Aberrant inflammatory reaction is one of the hallmarks of aging and the recruitment of MDSCs appears to potentially link inflammatory cells with cancer. In tumors, MDSCs were engaged to inhibit cytotoxic T cell responses, but activate regulatory T cells and macrophages through cytokines IL-6 and IL-10 expression. In line with this evidence, cholangiocarcinoma patients harbored remarkably higher population of monocytic MDSCs (M-MDSCs, defined as CD11b+ CD14+/HLA-DR-) than healthy controls, suggesting that MDSCs act to promote the growth of BTC.

Dendritic cells (DCs) play active roles in the adaptive immune responses via activating the T cells and inhibiting checkpoint expression. Increased CD83+ DCs were correlated with enhanced infiltration of CD4+/CD8+ T cells and the better outcomes in cholangiocellular carcinoma. Downregulation of FcεRI+ monocytes and DCs was found in the peripheral blood of hepatocellular carcinoma and cholangiocarcinoma patients. Activation of CD40, a cell-surface member of the TNF receptor family, facilitated the activation of DC-mediated cytotoxic T-lymphocyte (CTL) and suppressed TAMs. A CD40 agonist CDX-1140 is currently used in a phase I clinical trial in solid tumors including BTC (NCT03203876, as a safety study of Lirilumab in combination with Nivolumab or in combination with Nivolumab and Ipilimumab in advanced and/or metastatic solid tumors at Local Institution, Kashiwa-shi, Chiba, and Local Institution Kobe-shi, Hyogo, Japan). This immunotherapy aiming at different immune molecules involves Lirilumab, an anti-KIR monoclonal antibody, Nivolumab, an anti-PD-1 monoclonal antibody, and Ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody.

Tumor-infiltrating lymphocytes (TILs) emerge as key function in tumorigenesis. TILs consist of B lymphocytes, cytotoxic T cells (CD8+), and T helper cells (CD4+T). CD4+ TILs expressing mutated ERBB2 interacting protein (ERBB2IP) with loss of tumor suppression were identified in the development of BTC. In contrast, increased CD8+ TILs protected tumor growth and were correlated with better overall survival (OS) of BTC patients. Decreased expression of FoxP3, a transcription factor expressed by Tregs, restricted tumor invasion and immune escape in cholangiocarcinoma by downregulation of TGF-β1, as FoxP3 upregulated expression of PD-L1, the immune checkpoint. Blockade of PD-L1 by PD-L1 antibodies was associated with favorable prognosis in pancreatic ductal adenocarcinoma. A broad spectrum of evidence established the notion that overexpressed PD-L1 expression in BTC patients was correlated with poor outcomes. In concert with these findings, our group recently demonstrated that genomic ERBB2/ERBB3 mutations regulated PD-L1 expression that mediates immune escape of gallbladder cancer. CTLA-4 is one
of immune checkpoints, which specifically interacts with CD80. CTLA-4 and CD80 were upregulated in BTC patients. At present, there are several ongoing clinical trials mainly focusing on anti-PD-1 and anti-CTLA-4 therapy in BTC (NCT03473574, Durvalumab and Tremelimunab with Gemcitabine or Gemcitabine/Cisplatin compared to Gemcitabine/Cisplatin in CCA patients at Medizinische Hochschule Hannover, Klinik für Gastroenterologie, Hepatologie & Endokrinologie, Hannover, Germany; NCT03046862, Durvalumab [MEDI4736]/Tremelimumab in combination with Gemcitabine/Cisplatin in chemotherapy-naive BTC at Seoul National University Hospital, Seoul, Korea; NCT03704480, Durvalumab plus Tremelimumab combination immunotherapy with or without Wweekly Paclitaxel in patients with advanced BTC after failure of Platinum-based chemotherapy at CHRU Jean Minjoz, Besançon; Polyclinique Bordeaux Nord Aquitaine, Bordeaux; Hôpital Duchenne, Boulogne-sur-Mer; and other 25 institutes in France). In addition, a phase I clinical trial in combination therapy with glucocorticoid-induced tumor necrosis factor receptor (GITR) agonist TRX518 and pembrolizumab or nivolumab has been practiced in patients with advanced solid tumors (NCT02628574, phase 1 open-label study of TRX518 monotherapy and TRX518 in combination with Gemcitabine, Pembrolizumab, or Nivolumab at University of Chicago, Chicago, IL, USA; University of New Mexico Comprehensive Cancer Center, Albuquerque, NM, USA; University Hospitals, Cleveland, OH, USA; and other three institutes in the United States), based on the newly reported evidence revealing that blockade of GITR that was upregulated in TILs of BTC can eliminate Treg-mediated immune suppression.

3 THE CLINICAL CHALLENGE IN TREATMENT OF ELDERLY PATIENTS WITH BTC

Given the rapid development of advanced technology and divergent therapeutic means over the past decades, global human life increases and subsequently incidence of patients old than 75 years with various diseases notably rises. In 1990, in Japan almost 6000 cases of 13,770 BTCs (43%) were diagnosed in patients with age of 75 or older. By 2003, this incidence was increased to 58% in 11,401 BTC patients. As the age increases but antitumor capability (e.g., antitumor immunity) decreases, the disease can be anticipated to rapidly undergo malignant transformation, resulting in the failure of multiple therapeutic intervenes. There is currently lack of a standard regimen that can be engaged for routine treatment of patients with BTC at the age of 75 or older, as most of chemotherapeutic and targeted drugs are not well tolerated. Therefore, the effective treatment specific for this large vulnerable subpopulation in BTC should be deliberately taken into account.

3.1 The treatment of surgery for elderly BTC patients

Radical resection is a century-old but still powerful approach that can effectively treat BTC. Anne Horgan et al. attempted to simply compare outcomes for patient age <70 to age ≥70 following surgery of 322 patients out of 913 BTCs. Unfortunately, the different ages did not yield impacts on disease survival, as the elderly (38%) and younger (39%) patients of 322 cases showed the same survival, although disease early stage (stage I/II) and Eastern Cooperative Oncology Group performance status (ECOG PS) < 2 were associated with surgical intervention in younger and elderly group, respectively.

Fabian Bartsch classified 150 BTCs into two subsets with age of <70 (n = 99) and >70 (n = 51). They found that recurrence-free survival (RFS) of BTC in age of <70 was significantly better than patients with age of >70 (P = 0.047), while OS showed the tendency of significance (P = 0.072). However, when the authors further divided the young group (<70 years old) into 30–50 (n = 23) and 50–70 (n = 76) years old groups, they did not find significant difference of OS (P = 0.076) and RFS (P = 0.179) between the two groups. Likewise, the groups with age between <50 and >70 did not give rise to the difference of OS (P = 0.931) and RFS (P = 0.845).

In a multicenter study, Alessandro Vitale did the similar study with 129 older (>70 years) and 455 younger (<70 years) patients and found that the elderly patients had a higher incidence of general complications (52.7% vs. 42.6%; P = 0.03) and major complications (24.0% vs. 14.9%; P = 0.01), but 30-day (0.1% vs. 3.3%; P > 0.05) and 90-day (2.3% vs. 5.5%; P > 0.05) mortalities were comparable. Five-year OS and disease-free survival (DFS) were comparable between the two sets (OS, 13.3% vs. 24.4%; DFS, 7.3% vs. 12.0%; P > 0.05). On propensity score matching analysis, DFS and OS were also comparable between the two different age patients. Interestingly, in the elderly group, poor tumor grade was associated with worse DFS (hazard ratio [HR] = 1.6, 95% confidence interval [CI]: 1.0–2.6; P = 0.04), whereas periductal invasion (HR = 1.9, 95% CI: 1.1–3.5; P = 0.03) and nodal disease (HR = 2.3, 95% CI 1.3–3.9; P = 0.003) were correlated with DFS in the younger patients. Therefore, substantial studies with larger cohorts from different cancer centers will be crucial for the establishment of relationship between age and clinical outcome in BTC.
### TABLE 1  Summarized clinical trials in the elderly BTC patients

| Drug investigated         | Target population | Phase | Clinical trial ID          | Country   | Reference |
|---------------------------|-------------------|-------|----------------------------|-----------|-----------|
| Cisplatin                 | BTC               | II    | NCT00380588                | Japan     | 105       |
| Gem                       | BTC               | II    | /                          | Japan     | 106       |
| Gem, cisplatin, and/or combination | BTC | Retrospective study | /                        | Japan     | 98        |
| Gem                       | Cycle in pancreatic or biliary cancer patients | Retrospective study | /                        | Japan     | 107       |
| Pemigatinib               | iCCA              | II    | NCT02924376                | USA       | 110–112   |

#### 3.2  The effectiveness of chemotherapy for elderly BTC patients

Gem and Cisplatin are considered as an effective first-line chemotherapy for the treatment of BTC. However, elderly BTC patients with cardiac and renal disease are usually not instructed to receive Ciplatin. Whether the combination of Gem and Cisplatin is an appropriate option for these subjects remains to be evaluated. In BT22 trials, 84 BTC patients with a median age of 65.2 were recruited to take Cisplatin at a low dose (25 mg/m²) with a 3-week course of day 1 and 8 treatment. During this trial, the most common adverse incidence with grade 3 and 4 level included decreased hemoglobin and erythrocytes and thrombocytopenia. Analyses on drug tolerance and efficacy in the elderly population were not performed, although these cohorts involved elderly patients up to the age of 85. Kuriyama (Table 1) enrolled 28 elderly patients (≥70 years) with unresectable BTC to receive Gem. After treatment with Gem, nine cases (69.2%) were stable and two patients (15.4%) were progressive, suggestive of a high disease control rate. The median OS for GEM-treated group and nontreated BTC was 9.1 and 2.9 months, respectively, and the 1-year survival rate was 15.4% and 6.7%, respectively. Grade 3 and 4 level of neutropenia occurred in three cases (23.1%), leukopenia in two cases (15.4%), and anemia in one patient (7.7%). Grade 3 nonhematologic toxicities included constipation (7.7%) and fatigue (7.7%). Although extensively more patients are essential to validate this finding, this study at least in part has suggested that chemotherapy with single-agent Gem is a safe and well-tolerated regimen for elderly BTC patients.

In other clinical trials, no difference of clinical outcomes and drug side effects between old and young age was observed. For example, Tadayuki Kou (Table 1) retrospectively evaluated 403 BTC patients who received palliative chemotherapy containing Gem, Cisplatin, and/or combination. A total of 309 patients (<75 years) were classified as a younger group and 94 cases (≥75 years) as an elderly group. Tumor control was achieved in 46 of 94 patients (48.9%) in the elderly group and 153 of 309 patients (49.5%) in the other group (P = 0.92). The drug response was 11.7% and 12.6% in the two groups (P = 0.81). Accordingly, the median OS was 10.4 (95% CI: 8.6–12.2) and 11.5 months (95% CI: 10.3–12.4) in the two groups (HR = 1.14; 95% CI: 0.89–1.45; P = 0.31). Furthermore, the frequency of adverse events was identical, although the incidence of interstitial pneumonitis was significantly higher in the elderly group.

Seigo Yukisawa et al. (Table 1) reported the outcomes and tolerance of systemic chemotherapy that included intravenous injection of Gem at a dose of 1000 mg/m² on days 1, 8, and 15 of a 4-week cycle in pancreatic or biliary cancer patients. A total of 102 patients including 29 BTCs were involved. They found that the frequency of any grade 3 or 4 toxicities and severe adverse events was not significantly different between the elderly (>75 years) and the younger patients (<75 years) of BTC. The median OS days between the two groups were no statistical different. The results demonstrated that full-dose chemotherapy with Gem for BTC is feasible in the younger and elderly patients.

#### 3.3  Impact of targeted therapy on elderly BTC patients

A wealth of basic research evidence has revealed multiple key molecules that drive or participate in the development of BTC; thus, a variety of gene-targeted drugs have been settled in clinical trials. These targets include isocitrate dehydrogenase-1 (IDH-1) mutations, RAS-dependent mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase (PI3KCA)/Akt/mTOR and fibroblast growth factor receptor (FGFR) fusions and rearrangements. Unfortunately, most elderly patients were unable to complete an entire course of clinical trials mainly due to unexpectedly rapid cancer malignant progression; therefore, very limited studies with gene-targeted drug trials specific for elderly BTC were documented.

In the open-label, multicenter, FIGHT-202 trial (Table 1), 5% of patients (5/107) with age ≥75 years old and 19% (20/107) with age between 65 and 75 years old
in iCCAs were used for FGFR2-targeted therapy, based on FGFR2 fusions or rearrangements. Two out of five patients with age ≥75 in iCCAs responded to the therapy which ORR (objective response rate) is 40%. A slightly lower ORR (34.1%) was highlighted in patients with aged ≤ 65 years old. However, given the insufficient case volume, the estimated comparisons failed to yield difference between these patient populations.

4 | SUMMARY

Elderly BTC patients are the main population of BTCs. At present, however, there is lack of clinical investigations characterizing the difference of disease symptoms and therapeutic approaches between elderly and younger patients. As the global human life increases, the aging constitutes the primary risk factor of BTC. The high incidence of disease relapse and malignancy remains static. Of note, a variety of molecular and cellular factors in TME that are distinctive in these varied ages suggest that these age-related dissimilarities may account for the central pathogenetic elements in the development of elderly BTC. However, we currently still lack effective means to specifically treat this vulnerable population. Therefore, it is of paramount importance to systematically set up multicenter, case–control clinical trials with chemotherapy, gene-targeted therapy, immunotherapy, and/or combination therapy in elderly BTCs. The effective regimen will be essential for the ultimate improvement of patient life quality.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
Yingbin Liu conceptualized the idea of the study, administered the project, and reviewed and edited the manuscript.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable as no new data were created or analyzed in this study.

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