Editorial Commentary

Conversion therapy for advanced cholangiocarcinoma in the era of molecular targeted therapy and immune therapy

Zunyi Zhang[1,2,3]^, Wei Zhang[1,2,3]^

[1]Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [2]Hubei Clinical Research Center for Hepatic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [3]Hubei Key Laboratory of Hepato-Pancreato-Biliary Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Correspondence to: Wei Zhang, MD. Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Hubei Clinical Research Center for Hepatic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Hubei Key Laboratory of Hepato-Pancreato-Biliary Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan 430030, China. Email: weizhangtjh@hust.edu.cn.

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Cholangiocarcinoma (CCA) encompasses a range of neoplasms, namely intrahepatic CCA, perihilar CCA, and distal CCA, which are distinguished by their anatomical origin. In cases where radical resection of CCA is feasible and the patient's physical condition permits surgical intervention, it is advisable to proceed with surgical treatment (1). However, the insidious onset of the disease restricts surgical candidacy to only 20–30% of patients (2,3). For those with unresectable CCAs, the recommended initial treatment is gemcitabine plus cisplatin (GemCis) chemotherapy (4). However, the GemCis chemotherapy regimen has been found to yield a relatively modest average survival time of 11.2 months and a limited objective response rate (ORR) of 26.1%. In response to these challenges, a novel approach known as conversion therapy has emerged as a potential strategy for managing unresectable tumors, initially proposed in hepatocellular carcinoma (HCC) patients. This approach aims to reduce tumor burden through a combination of locoregional or systemic therapy, ultimately rendering patients amenable to surgical resection. Notably, conversion therapy has also been mentioned in the context of CCA. Encouragingly, after undergoing successful conversion surgery, patients with advanced CCA have demonstrated a remarkable 2-year survival rate of 88% and the average survival time of 46 months (5). The issue pertaining to conversion therapy is that the conversion rate is unsatisfactory with standard GemCis therapy for advanced CCA. Recent published clinical trials of standard GemiCis chemotherapy for advanced CCA revealed that almost no patients were successfully converted and underwent surgical resection. Consequently, there exists an imminent necessity for novel treatment approaches or combination therapies to enhance the conversion rate and ultimately ameliorate the prognosis for advanced or unresectable CCAs.

The recent advent of molecular testing and next-generation sequencing has led to the delineation of the genetic landscape of CCA. Several clinical trials have evaluated the efficacy of novel targeted agents against CCA with certain molecular alterations, including isocitrate dehydrogenase (IDH) 1, fibroblast growth factor receptor (FGFR)-2 and neurotrophic tyrosine receptor

^ ORCID: Zunyi Zhang, 0000-0002-0370-1596; Wei Zhang, 0000-0002-3380-1010.

kinase (NTRK). In December 2016, silmitasertib, an oral small molecule casein kinase 2 (CK2) inhibitor, was granted Orphan Drug Designation by the US Food and Drug Administration (FDA) for the treatment of CCA. In Mar 1, 2023, a phase 1b/2 study (S4-13-001) aimed to investigate safety and efficacy of silmitasertib plus GemCis chemotherapy versus GemCis in locally advanced/metastatic CCA was published in *Hepatology* (5). According to this published data, phase 1b study confirmed that the maximum tolerated dose (MTD) of silmiltasertib was 1,000 mg twice daily, which was then used in the expansion and exploratory cohorts. In phase 2 study, this trial met its primary end point of estimated median progression-free survival (PFS) in favor of combination silmiltasertib and GemCis (11.2 *vs.* 5.7 months; P=0.0496). Moreover, an improvement in overall survival (OS) was detected in favor of combination silmitasertib and GemCis (17.4 *vs.* 14.9 months). Furthermore, the combination of silmitasertib and GemCis demonstrated an elevated ORR compared to the GemCis alone (34% *vs.* 30.8%). No patients receiving successful conversion surgery after combination treatment have been reported. The overall toxicity levels were similar between the two arms. Overall, this phase 1b/2 study shows that combination of silmitasertib and GemiCis chemotherapy may improve survival in advanced CCA without new safety signal.

Based on the available published data, several considerations can be drawn. Firstly, the achievement of a high ORR and a lower tumor stage within a short timeframe are crucial factors for the successful implementation of conversion therapy. Recent clinical trials examining the efficacy of standard GemiCis chemotherapy in advanced CCA have reported an ORR ranging from 15–26.1% (6,7). This unsatisfactory ORR of GemCis chemotherapy poses challenges in promoting conversion therapy. Given the significant resistance to chemotherapy and low survival rates, numerous novel agents are currently being investigated in clinical trials. The addition of S-1, an oral fluoropyrimidine combination comprising tegafur, gimeracil, and oteracil, to GemCis chemotherapy resulted in a significant improvement in ORR to 41.5%. Among the 119 patients receiving combined therapy, three underwent conversion surgery, whereas no patients in the GemCis group underwent conversion surgery (6). In another real-world study assessing the efficacy and safety of nab-paclitaxel plus GemCis in advanced CCA, the ORR was found to be 47.9%, with a total of 20 patients (11.2%) undergoing conversion surgery (8). Recently, gemcitabine and cisplatin plus durvalumab for patients with advanced biliary tract cancer (BTC) has been evaluated in the phase 3 TOPAZ-1 study (9). Six hundred and eighty-five patients with inoperable, locally advanced, recurrent, or metastatic BTC were randomly assigned to receive durvalumab or a placebo. OS and PFS was significantly improved for the durvalumab group. ORR was 26.7% for durvalumab and 18.7% for placebo. However, the conversion rates were not reported. Furthermore, a combination of angiogenesis/checkpoint blockade with chemotherapy may further enhance anti-tumor immune responses. Lenvatinib is a multiple multi-target receptor tyrosine kinase (RTK) inhibitor targeting VEGFR1-3, FGFR1-4, and PDGFRα. In a phase II trial (NCT03951597), the combination of toripalimab and levatinib plus gemcitabine and oxaliplatin (GEMOX) was evaluated as a first-line therapy for locally progressed or metastatic ICC (10). The ORR was 80% (24/30) and disease control rate (DCR) was 93.3% (28/30) among the 30 enrolled patients. Three patients with locally advanced disease received resection after being successfully downstaged. In Borad's study, the combination of silmitasertib and GemCis resulted in an elevated ORR of 34% compared with GemCis. Although the differences in OS and ORR were not statistically significant, one patient in the combination group achieved a complete response. The efficacy outcomes of silmitasertib combined with GemCis appear promising and comparable to other treatments. The potential for further improvement in efficacy may be realized by combining immunotherapy with silmitasertib and GemCis. With a higher ORR and longer PFS, this combination therapy holds promise as a viable option for conversion therapy.

Secondly, it is well-established that CCA is a highly aggressive form of malignant tumor characterized by significant heterogeneity. According to published data, the specific mutations observed in this disease can vary depending on the location of the tumor. In the case of intrahepatic CCA, the most commonly observed mutations include FGFR1-3 (fusion, mutation, and amplification) (11–45%), tumor protein p53 (TP53) (2.5–44.4%), IDH1/2 (4.9–36%), Kirsten rats arcomaviral oncogene homolog (KRAS) (8.6–24.2%), B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutation (3–7.1%), and epithelial growth factor receptor (EGFR) (1.5–2%). On the other hand, patients with extrahepatic CCA generally exhibit mutations in KRAS (8.3–42%), TP53 (40%), SMAD family member 4 (SMAD4) (21%), human epithelial growth factor receptor-2 (HER2) (17.4%), IDH1/2 (0–7.4%),

and BRAF (3%) (11). Therefore, the efficacy of the same therapy may vary between intrahepatic and extrahepatic CCA due to differences in mutation gene types. Selecting the appropriate therapy for individual patients with CCA is crucial for improving efficacy and conversion rates. For instance, FGFR abnormalities play a significant role in the development of intrahepatic CCA, whereas the mutation rate is low in extrahepatic CCA. In the FIGHT-202 study, pemigatinib alone demonstrated an ORR of 35.5% in advanced CCA patients with FGFR2 rearrangement and fusion mutation. It was found that 98% of the patients with intrahepatic CCA demonstrated effectiveness (12). Among the 107 patients with advanced CCA, two cases achieved tumor downstaging and subsequently underwent successful surgery, resulting in a conversion rate of 1.8%. In Borad's study, the overexpression of CK2 in the analysis of The Cancer Genome Atlas (TCGA) database suggests that it may not serve as a reliable biomarker for predicting prognosis. However, it is imperative to exercise caution when interpreting these data. Additional investigations are warranted to validate the expression status of CK2 or determine the genomic subgroup. Furthermore, the identification of novel gene biomarkers, in addition to CK2, is essential for accurately predicting the effectiveness of silmiltasertib. The discovery of the new biomarkers has the potential to significantly enhance treatment efficacy and conversion rates.

In conclusion, the study conducted by Borad *et al.* demonstrates that the utilization of silmitasertib in combination with GemCis chemotherapy yields remarkable efficacy in the treatment of advanced CCA. This finding presents a potential alternative for conversion therapy or as first-line treatment option for unresectable CCA. However, it is imperative to conduct additional clinical trials to identify the appropriate biomarker and new combination of treatments to enhance the overall effectiveness of this treatment.

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