American Journal of Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Case Report

Successful Conversion Therapy with TACE Plus Olaparib in Advanced Intrahepatic Cholangiocarcinoma: A Case Report

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To Cite This article: *Tiezhong Zhang, Lijie Zheng and Zongli Zhang*, Successful Conversion Therapy with TACE Plus Olaparib in Advanced Intrahepatic Cholangiocarcinoma: A Case Report. Am J Biomed Sci & Res. 2026 30(3) AJBSR.MS.ID.003929,*

DOI: 10.34297/AJBSR.2026.30.003929

Received: February 16, 2026; **Published:** March 06, 2026

Abstract

Background: The management of initially unresectable Intrahepatic Cholangiocarcinoma (iCCA) remains a formidable challenge. Conversion therapy aims to downstage tumors to enable radical resection. However, it remains investigational for iCCA, with no established standard.

Case Presentation: We report a case of advanced iCCA treated with Transarterial Chemoembolization (TACE) combined with the poly adenosine diphosphate-ribose Polymerase Inhibitors Inhibitor (PARPi) olaparib as conversion therapy. The patient underwent radical hepatectomy, which culminated in an R0 resection. Postoperative pathological examination revealed complete tumor necrosis, indicative of a Pathological Complete Response (pCR).

Conclusion: Based on the findings from this case, we consider that patients with iCCA harboring mutations in other DNA repair genes, such as MSH2, MSH6, CDK12, and HDAC2, may still derive benefit from conversion therapy with olaparib, even in the absence of detected pathogenic mutations in canonical Homologous Recombination Repair Deficiency (HRD) core genes like BRCA1/2. Although the specific genomic driver in this instance remains to be fully elucidated, this case expands the treatment landscape for iCCA. However, this conclusion warrants further validation in larger cohorts.

Keywords: Intrahepatic cholangiocarcinoma, Conversion therapy, Olaparib, DNA damage repair, curative surgical resection

Introduction

Intrahepatic Cholangiocarcinoma (iCCA) is a highly aggressive malignancy originating from the intrahepatic bile duct epithelium [1]. It constitutes the second most common primary hepatic cancer, with global incidence rates having increased steadily over recent decades [2]. Owing to the nonspecific early symptoms and the lack of reliable screening biomarkers, most patients are diagnosed at an advanced stage, rendering them ineligible for curative surgical resection [2]. For patients with initially unresectable or metastatic disease, systemic chemotherapy remains the cornerstone of treatment, albeit with modest survival benefits. Significant advancements have been made in the systemic management of iCCA in recent years. Targeted therapy and immunotherapy have opened new prospects for the treatment of advanced iCCA [3-5]. While these novel approaches have improved patient survival to a certain extent, the efficacy achieved thus far remains limited. Conversion therapy, as a crucial component of comprehensive treatment, aims to transform initially unresectable tumors into resectable ones [6]. In iCCA, however, conversion therapy remains investigational, with no standardized regimen established.

The efficacy of the poly adenosine diphosphate-ribose polymerase inhibitors inhibitor (PARPi), particularly olaparib, has been established in various solid tumors, especially those harboring BRCA pathogenic mutations [7,8]. However, iCCA patients harboring BRCA pathogenic mutations are relatively rare, accounting for only about 4% [9]. Consequently, the application of PARPi in iCCA is limited, with insufficient evidence regarding their efficacy. Herein, we report a case of initially unresectable iCCA without detected BRCA1/2 mutations, which achieved a Pathological Complete Response (pCR) following conversion Therapy Combining Transarterial Chemoembolization (TACE) and olaparib, ultimately leading to successful radical resection.

Case Presentation

A 65-year-old male patient presented on 21 September 2022 with a one-week history of jaundice. Abdominal Computed Tomography (CT) scan characterized a large left hepatic lobe tumor with features indicative of intrahepatic metastasis and regional lymphadenopathy, accompanied by biliary obstruction (Figures 1A, B). An ultrasound-guided liver biopsy was performed, and histopathological examination confirmed adenocarcinoma, consistent with cholangiocarcinoma (Figure 2E). Based on these findings, the final clinical diagnosis was stage IIIB (cT4N1M0) iCCA according to the 8th edition of the AJCC.

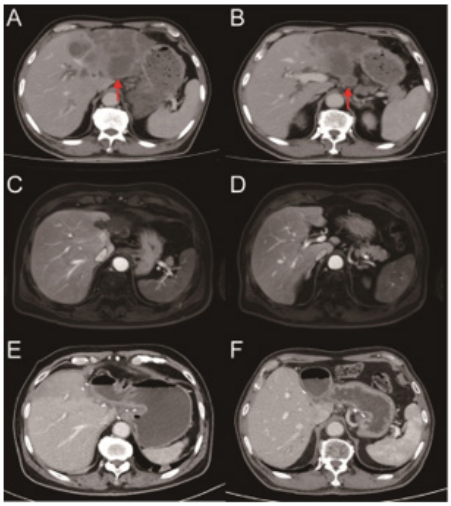

Figure 1: Serial computed tomography imaging assessments during conversion therapy. (A, B), baseline imaging in September 2022. The red arrows indicate the primary liver tumor and the enlarged lymph nodes at the hepatic hilum. (C, D), preoperative imaging in May 2024. (E), postoperative imaging in June 2024. (F), latest follow-up imaging in December 2025.

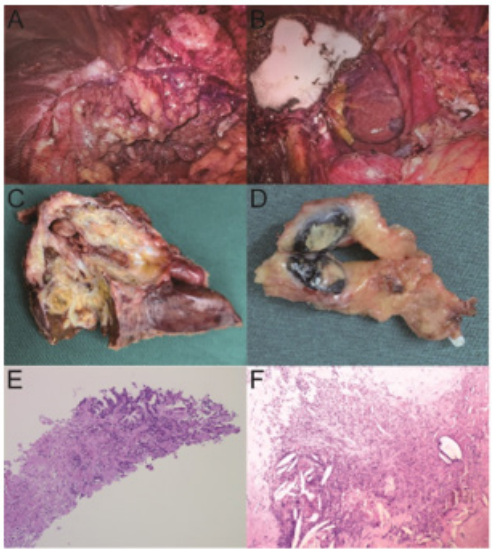

Figure 2: Laparoscopic surgical view and and specimen photograph. (A) Intraoperative view of the tumor site following conversion therapy. (B) Residual liver parenchyma and resection margin after hepatectomy. (C) Cross-sectional view of the resected left hemihepatectomy specimen. (D) Cross-sectional view of a dissected regional lymph node. (E) H&E staining (100×) of the baseline biopsy tissue. (F) H&E staining (100×) of the surgically resected tissue.

To alleviate the biliary obstruction, an Endoscopic Retrograde Cholangiopancreatography (ERCP) with stent placement was successfully performed on September 30, 2022. Given the advanced stage and the goal of disease control with potential conversion, the Multidisciplinary Team (MDT) decided on a combined modality approach. The patient underwent two sessions of Transarterial Chemoembolization (TACE) targeting the left hepatic lobe tumor on October 19 and November 30, 2022. Each TACE session was performed using a chemotherapeutic regimen consisting of 50 mg of lobaplatin, 10 mg of idarubicin, and 4 mg of raltitrexed. The results of the Next-Generation Sequencing (NGS) were as follows: HDAC2 (exon 1, p. V12Sfs*20, VAF: 27.88%); MSH2 (exon 4, p. A230Lfs16, VAF: 24.03%); MSH6 (exon 5, p. F1088Sfs2, VAF: 24.07%); CDK12 (intron 6, c.2610-1G>A, VAF: 4.42%). Prompted by the NGS findings, specifically the presence of mutations in DNA Damage Repair (DDR) genes, the patient was started on olaparib (300 mg orally twice daily) in October 2022 (Figure 3).

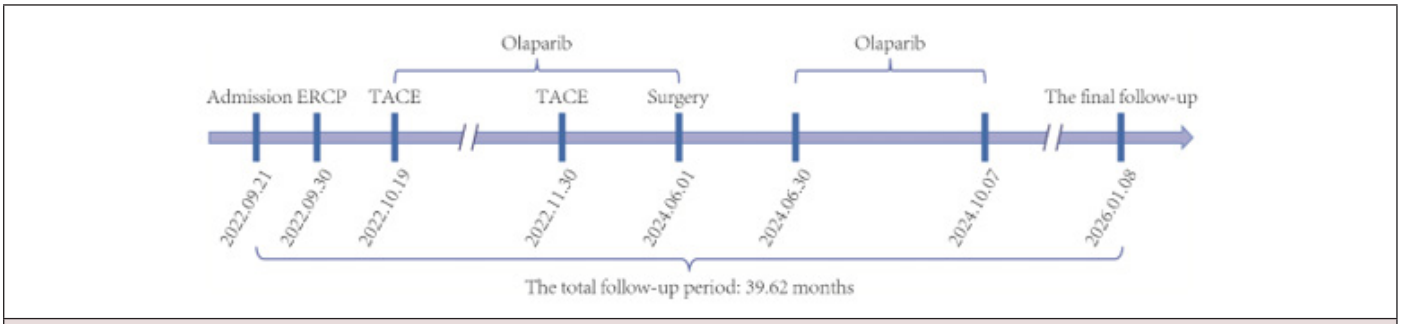

Figure 3: Timeline of treatment and follow-up. This schematic illustrates the key therapeutic interventions and clinical milestones for the patient with advanced iCCA. The conversion therapy period, defined as the interval from the initiation of combined TACE and olaparib to curative surgery, spanned 19.55 months. The total follow-up period from was 39.62 months.

The patient tolerated the combined regimen well. Serial imaging assessments documented a remarkable radiological response. After 19.55 months of treatment with maintained excellent performance status (ECOG 0), restaging imaging in May 2024 confirmed significant tumor downstaging (Figure 3). The MDT re-evaluated and deemed the disease resectable (Figures 1C, D). On June 1, 2024, the patient underwent a laparoscopic left hemihepatectomy with cholecystectomy and regional lymphadenectomy (stations 1, 3, 7, 8, 9, 12 and 13). The procedure was completed successfully with R0 resection margins (Figures 2A, B). Furthermore, no viable tumor cells were identified in the primary tumor bed or in any of the resected regional lymph nodes (0/7), fulfilling the criteria for a Pathological Complete Response (pCR) (Figures 2F). The patient's postoperative recovery was uneventful. Olaparib was resumed one month after surgery and was discontinued in October 2024 after a total treatment duration (Figures 2C, D). Regular surveillance with imaging and tumor markers has been conducted. As of the last follow-up in January 2026, the patient remains asymptomatic with an excellent performance status (ECOG 0), and shows no evidence of disease recurrence (Figures 1F).

Discussion

This report presents a paradigm-shifting case in which a patient with initially unresectable iCCA, lacking canonical BRCA1/2 mutations, achieved a pCR following conversion therapy with TACE and the PARPi olaparib. Firstly, this outcome directly challenges the conventional biomarker-driven paradigm for PARPi use and illuminates a potential therapeutic avenue for a broader subset of iCCA patients. The cornerstone of this case is the profound pathological response. The finding of no viable tumor cells in the resected specimen, coupled with the sustained radiological and serological response, unequivocally demonstrates the efficacy of the chosen regimen. This case carries significant clinical implications. Secondly, it highlights the critical importance of MDT driven, personalized strategy in managing advanced iCCA. The sequential application of biliary drainage, locoregional therapy, and precisely timed systemic targeted therapy was instrumental in this success.

The central scientific inquiry revolves around the molecular basis for olaparib sensitivity in the absence of BRCA1/2 mutations. NGS analysis revealed a complex molecular profile with mutations in CDK12, HDAC2, MSH2, and MSH6. We posit that the CDK12 mutation is the most plausible contributor to the observed HRD phenotype and subsequent olaparib sensitivity. CDK12 is a key regulator of transcription for numerous DNA repair genes, including several core HRR components [10]. Its functional loss can induce a BRCA ness or functional HRD state, which has been clinically validated as a predictor of PARPi response in cancers like prostate and ovarian carcinoma [8,10]. The role of the concurrent MSH2 and MSH6 mutations, indicative of a Mismatch Repair (MMR) deficient state, is more complex. While MMR deficiency primarily confers sensitivity to immune checkpoint inhibitors, preclinical models and emerging clinical observations suggest potential crosstalk between MMR and HRR pathways [11-13]. It is conceivable that the co-occurrence of MMR deficiency and a CDK12 mediated functional HRD created a uniquely profound genomic instability, amplifying tumor vulnerability to DNA damaging agents and PARPi

[11]. The HDAC2 mutation adds another layer of complexity, as epigenetic modifiers like HDAC2 can globally influence DNA repair gene expression [14,15]. This case illustrates that therapeutic sensitivity may not stem from a single driver alteration but from the aggregate effect of multiple DDR gene disruptions, a concept we term "composite DDR deficiency."

The limitations of this single-case report are acknowledged. The precise mechanistic contribution of each mutation remains hypothetical, and the generalizability of this approach needs validation. Furthermore, the optimal sequence and combination of TACE with olaparib require systematic study (Figure 4).

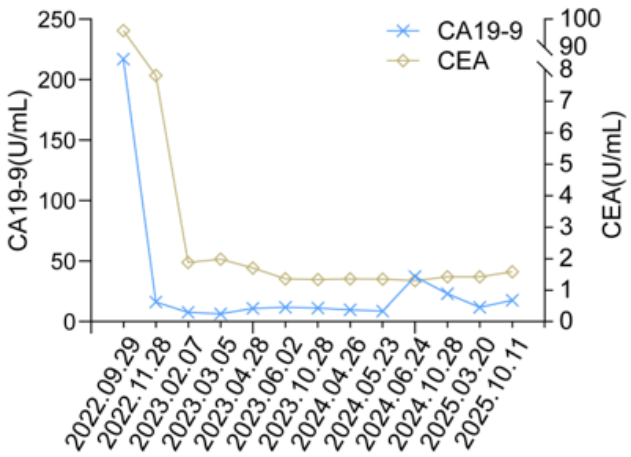

Figure 4: Line graph of serum tumor markers. This graph illustrates the dynamic changes in serum CEA (brown line, right y-axis) and CA19-9 (blue line, left y-axis) levels throughout the treatment course.

Conclusion

In conclusion, this case provides compelling evidence that a subset of iCCA patients without BRCA1/2 mutations can derive exceptional, potentially curative benefit from PARPi based conversion therapy. The observed pathological complete response was likely facilitated by a functional HRD state, potentially initiated by a CDK12 mutation and amplified by a broader composite DDR deficiency involving MMR and epigenetic pathways. This success story underscores the necessity of comprehensive molecular profiling to uncover hidden therapeutic vulnerabilities in iCCA. It advocates for the consideration of olaparib, particularly in combination with locoregional strategies, as a viable conversion therapy option for select patients with DDR pathway alterations. Prospective clinical trials are urgently warranted to define the predictive biomarkers, efficacy, and safety of this promising therapeutic strategy in advanced biliary tract cancers.

Authorship Contribution Statement

Tiezhong Zhang: Writing – original draft. Lijie Zheng and Zongli Zhang: Writing – review & editing.

Conflict of Interest

The authors declare that they have no competing interests.

Data Availability

No data was used for the research described in the article.

Acknowledgements

Not applicable.

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