Evolving approaches in advanced gallbladder cancer with complete pathological response using chemo-immunotherapy: A case report

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Abstract. The combination of chemotherapy and immunotherapy for metastatic cholangiocarcinoma (CCA) offers promising improvements in survival and response rates beyond traditional treatments. TOPAZ-1 and KEYNOTE-966 have demonstrated the efficacy of combining immunotherapy (durvalumab and pembrolizumab) with chemotherapy, even in gallbladder cancer (GBC), with a complete response rate of 2.7% in the TOPAZ-1 trial. Advanced CCA treated with immunotherapy combinations has shown complete responses influenced by high programmed death-ligand 1 (PD-L1) or Epstein-Barr virus expression. These responses were enhanced by combining radiotherapy with programmed cell death protein 1 (PD-1) blockade. A 62-year-old man was diagnosed with unresectable GBC, distant lymphatic metastases, and local invasion of liver segments 4i and 5, the colonic hepatic flexure, the duodenal bulb, and the pancreatic head. Immunohistochemical examination revealed poorly differentiated squamous cell carcinoma, without expression of PD-L1. Next generation sequencing revealed the mutation of ERBB2 R678Q and a microsatellite stable tumour. The patient started chemo-immunotherapy with cisplatin-gemcitabine plus durvalumab in June 2022. After eight cycles, a significant reduction in tumour volume and markers was reported, and therapy with durvalumab was maintained through November 2023. The subsequent computed tomography scans showed further reduction in the tumour volume, and surgical resection was performed. Histological examinations confirmed the absence of residual tumour or lymph node metastases. As of June 2024, the patient has shown no signs of disease recurrence. Several reports of conversion surgery in GBC exist, but data on pre-surgical chemo-immunotherapy are limited. Furthermore, a complete response without pathological confirmation in CCA and GBC raises several questions regarding the need for surgery after immunotherapy. Although effective disease control and tumour regression have been reported in advanced GBC with combined anti-cytotoxic T-lymphocyte associated protein 4 and anti-PD-1 agents and chemotherapy, further studies are needed to identify reliable predictive biomarkers due to unclear associations with PD-L1 expression or tumour mutational burden. Overall, chemo-immunotherapy has been effective in treating metastatic CCA, especially when tailored to specific molecular profiles. These treatments may lead to complete responses and novel strategies.

Introduction

Gallbladder carcinoma accounts for the most common type of biliary tract cancer. While the incidence of gallbladder cancer (GBC) is relatively low, diagnosis often occurs at an advanced stage. Furthermore, surgery remains the only curative therapy for resectable diseases. For unresectable or metastatic diseases, the prognosis is poor, curative surgery is infeasible, and management has always been palliative because of the low response to traditional chemotherapy (1-3).

The recent advancements in chemo-immunotherapy, which integrates chemotherapy with immunotherapy, have improved the treatment's efficacy in terms of survival and response rates for metastatic cholangiocarcinoma, compared with conventional treatments (4). Studies (i.e., TOPAZ-1 and KEYNOTE-966) have evaluated the effectiveness of combining chemotherapy with immunotherapy agents (i.e., durvalumab and pembrolizumab, respectively) in intrahepatic or extrahepatic cholangiocarcinoma, including GBC (5,6). Both trials demonstrated the potential benefits of adding immunotherapy to standard chemotherapy regimens in treating biliary tract cancer at advanced stages, showing improvements in

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Abbreviations: CCA, cholangiocarcinoma; GBC, gallbladder cancer; MSS, micro satellite stable; NAT, neoadjuvant therapy; TMB, tumor mutational burden

Key words: GBC, chemo-immunotherapy, conversion therapy, pathological complete response

survival rates. In the TOPAZ-1 study, the combination therapy comprising durvalumab, gemcitabine, and cisplatin showed an overall response rate of 26.7% and a complete response rate of 2.7% (5). These findings underscore the importance of continued research and clinical trials to refine and enhance treatment protocols for improved patient outcomes. The integration of immunotherapy represents a promising shift in the treatment landscape, offering hope for improved long-term survival and quality of life for patients with advanced biliary tract cancers.

Some studies have aimed to identify the factors that predict which patients are more likely to achieve a complete response (7-10). These factors include molecular profiles such as PD-L1 expression, specific genetic mutations, and the presence of certain biomarkers. The findings suggest that a deeper understanding of tumour biology is necessary to tailor treatments more effectively, potentially leading to better outcomes. As the field of precision medicine evolves, incorporating molecular and genetic insights will be crucial in developing personalized treatment strategies for gallbladder cancer. Future research should also focus on identifying biomarkers that can predict response to therapy, enabling more targeted and effective treatment approaches. Furthermore, the role of combination therapies in overcoming resistance to single-agent treatments continues to be a critical area of investigation.

Case report

A 62-year-old male affected by GBC, unresectable at diagnosis, received chemo-immunotherapy and then underwent surgical resection with a pathological complete response. The events and treatments are summarised in the timeline shown in Fig. 1.

Informed consent was obtained from the patient for publication as a case description.

This patient had no significant medical history (only GERD and arterial hypertension were reported).

In April 2022, for persistent abdominal pain (particularly in the right hypochondriac region), the patient underwent an abdominal ultrasound, which revealed a large gallbladder neoplastic lesion. Computed tomography (CT) and magnetic resonance imaging (MRI) confirmed the presence of a gallbladder mass that extended to the liver, with suspected duodenal infiltration (Figs. 2 and 3). An esophagogastroduodenoscopy (EGD) was performed, and infiltration of the duodenum was excluded.

The case was discussed among the multidisciplinary board and an exploratory laparoscopy was performed 1 month later. Surgeons performed multiple biopsies of the gallbladder tumour infiltrating the hepatic pedicle and the head of the pancreas. Histopathological findings of the core biopsy revealed poorly differentiated squamous cell carcinoma that was negative for PD-L1 (SP263 IHC Ventana assay). Next generation sequencing was performed using the MiSeq Illumina platform and a Myriapod NGS Cancer panel DNA kit (Diatech), which revealed an ERBB2 R678Q mutation (NM_004448.4:c.2033G>A) with a VAF of 29%. The melting curve was analysed to evaluate microsatellite instability, showing that somatic DNA from the biopsy was stable (i.e., microsatellite stable). A subsequent CT scan was performed, showing a 97x93x120 mm mass extending from the gallbladder to liver segments 4i and 5, the colonic hepatic flexure, the duodenal bulb, and the head of the pancreas. Multiple perihepatic lymphadenopathies were also found.

Given the extent of the disease and the good performance status of the patient, we decided to start systemic therapy with cisplatin (25 mg/mq 1,8 q3w), plus gemcitabine (1,000 mg/mq 1,8 q3w), plus durvalumab (1,500 mg flat dose q3w), based on the results of the TOPAZ-1 trial, within an Expanded Access Program. At the beginning of therapy, CEA was 65.95 ng/ml and Ca19.9 was 5,113 U/ml.

Between June and December 2022, the patient received eight cycles of chemo-immunotherapy and exhibited excellent clinical, biochemical, and radiological responses. In particular, the patient reported an optimal improvement in abdominal pain, the reduction in markers was significant, and the CT scans performed in September and November 2022 showed significant reductions in the tumour volume, with an increase in the necrotic component. The therapy was maintained with durvalumab (1,500 mg q4w) starting in January 2023. The CT scan performed 2 months later showed further reduction in the neoplastic mass volume, and an EGD performed in February did not show tumour cells. After 3 months, in May 2023, the CT scan revealed further reduction in the gallbladder lesion (45 vs. 120 mm at the time of diagnosis), and the subsequent MRI confirmed the infiltration of the liver, with no certain cleavage plane with the duodenum or the hepatic flexure. On June 2023, CEA was 5.5 ng/ml and Ca19.9 was 8 U/ml. The patient maintained an excellent performance status and received durvalumab until November 2023. The CT scan performed after 9 months of treatment with maintaining durvalumab showed further reduction in the tumour volume, and thus the patient underwent surgical evaluation.

In December 2023, the patient underwent a laparotomy. A fibrotic mass extended from the gallbladder to the right colonic flexure and the second portion of the duodenum. The extemporaneous examination of 3 pericholecystic nodules and the cystic duct margin revealed no tumour cells. The fibrotic mass was detached from the colonic hepatic flexure and duodenum, revealing a cholecystoduodenal fistula, and the duodenum was sutured. The intraoperative ultrasound did not reveal the presence of liver lesions, and thus an extended cholecystectomy with en-bloc hilar lymphadenectomy and limited resection of liver segments 4i and 5 was performed. A histological exam revealed no residual tumour or lymph node metastases. The analysed mass showed the presence of chronic xanthogranulomatous inflammation, necrosis, and fibrosis without the presence of tumour cells. The postoperative course was complicated by sepsis, and a CT scan showed perihepatic fluid collection. The patient underwent CT-guided percutaneous drainage, and the microbial culture revealed Candida spp. Then, the patient was treated with fluconazole to resolve the abscess.

After surgery, the patient started close radiographic and clinical follow-up and has not shown a recurrence of the disease.

Discussion

The majority of GBC patients present advanced stages at diagnosis, precluding radical surgical options. Aggressive upfront

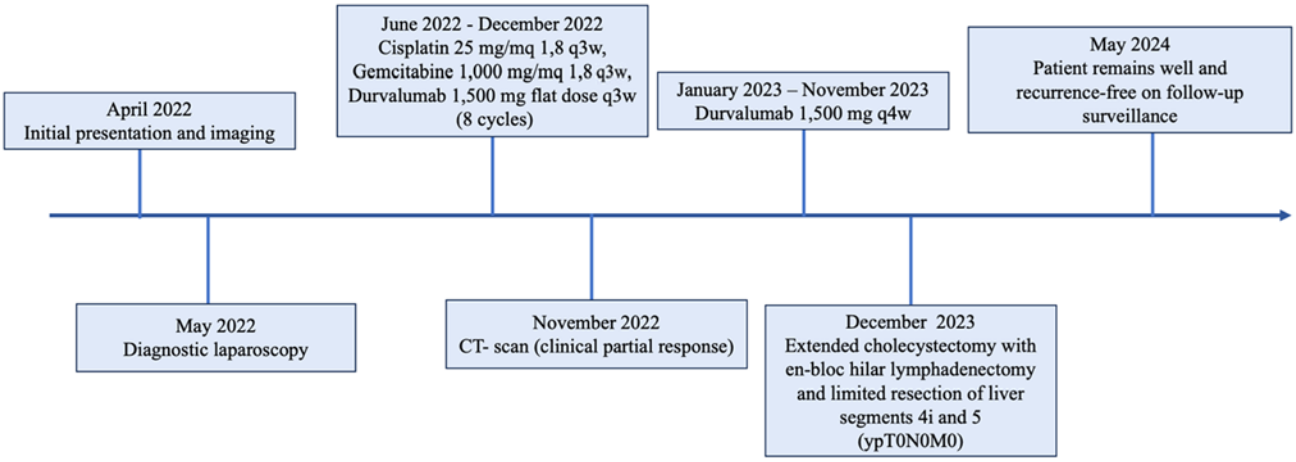

Figure 1. Timeline of patient treatment. 1,8 q3w, days 1 and 8 every 3 weeks; q3w, every 3 weeks; q4w, every 4 weeks.

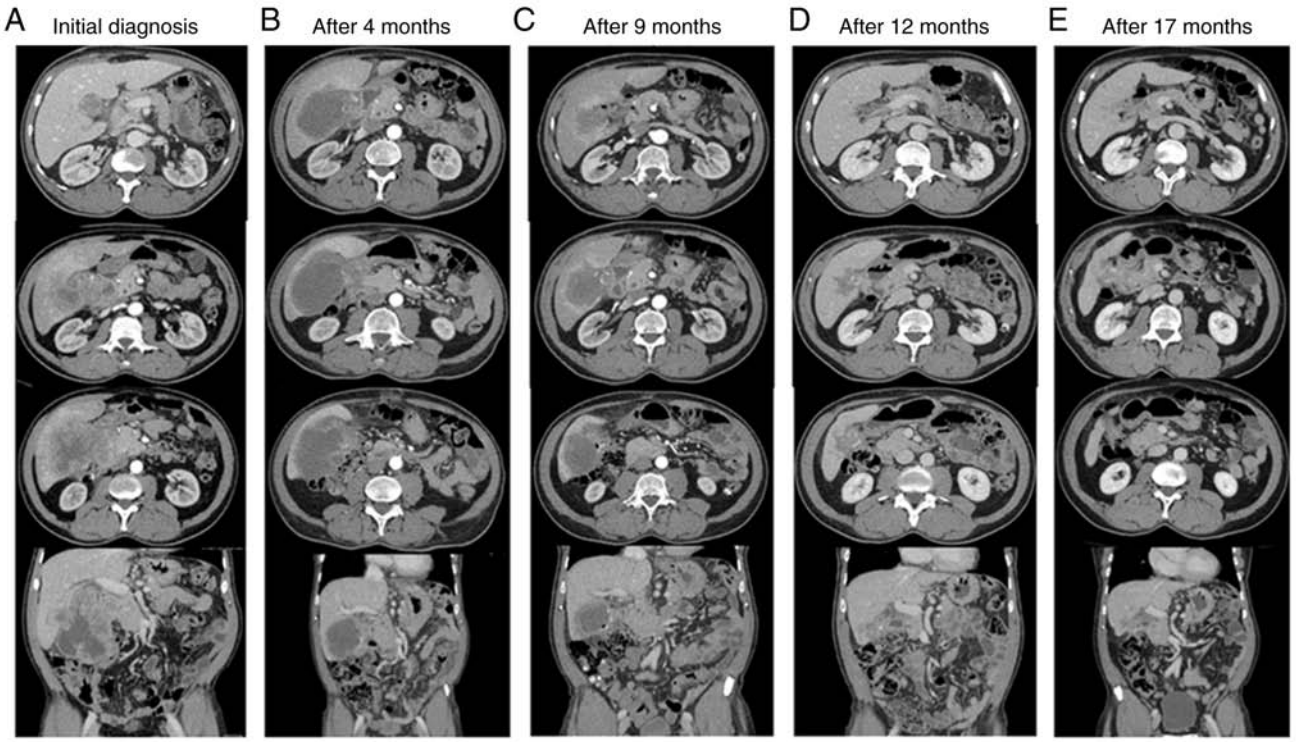

Figure 2. CT scan evolution over the course of 17 months of treatment. Enhanced CT scans showing a gallbladder lesion infiltrating the hepatic pedicle, the head of the pancreas, colonic hepatic flexure and liver lesions during the course of treatment, with a progressive reduction in the size of the lesion and the infiltrative component. (A) First three images: Axial CT scans showing the initial size of the lesion, infiltration of the hepatic pedicle, and impact on the head of the pancreas. Fourth image: Coronal CT scan highlighting the colonic hepatic flexure and liver lesions. (B) First three images: Axial CT scans showing a slight reduction in the lesion size, decreased infiltration of the hepatic pedicle and reduced impact on the head of the pancreas. Fourth image: Coronal CT scan showing less pronounced lesions in the liver. (C) First three images: Axial CT scans showing a marked reduction in lesion size, further decreased infiltration of the hepatic pedicle and minimal impact on the head of the pancreas. Fourth image: Coronal CT scan showing smaller liver lesions. (D) First three images: Axial CT scans showing the lesion was almost completely reduced, minimal to no infiltration of the hepatic pedicle and negligible impact on the head of the pancreas. Fourth image: Coronal CT scan showing near resolution of liver lesions. (E) First three images: Axial CT scans showing the lesion was almost completely reduced, minimal to no infiltration of the hepatic pedicle and negligible impact on the head of the pancreas. Fourth image: Coronal CT scan showing near resolution of liver lesions.

surgeries with extended resections do not benefit higher-stage GBC owing to the greater incidence of morbidity and mortality without oncological benefit (11). In this context, systemic therapies have gained attention, and over the past few years, the therapeutic landscape for unresectable GBC has evolved significantly. Historically, gemcitabine and cisplatin (12), or oxaliplatin when cisplatin is contraindicated (13), have been used in standard first-line chemotherapy regimens.

The role of neoadjuvant therapy (NAT) for GBC has not been clearly defined. The justification for using NAT is its potential to eliminate micro-metastases, decrease the size of the main tumour, expand the number of patients suitable for

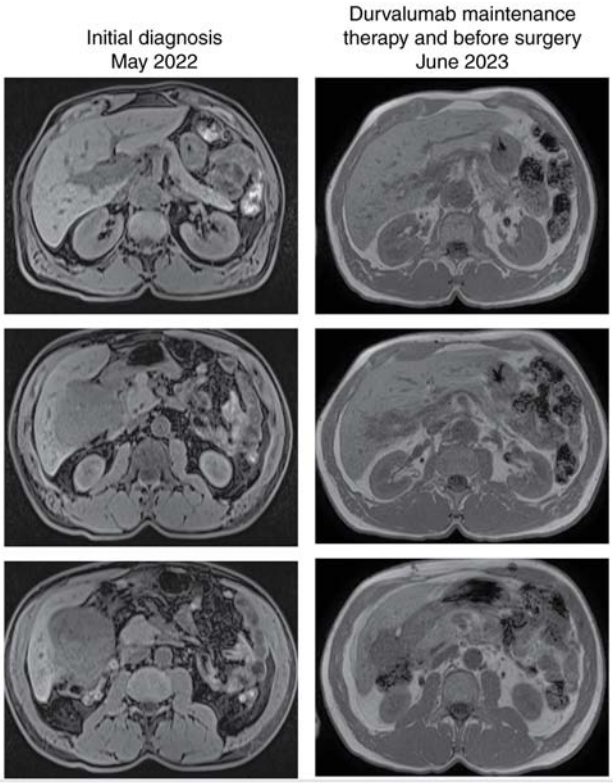

Figure 3. MRI before and after 12 months of chemo-immunotherapy. At the initial diagnosis, the three images in the left column are axial MRI scans. The first image shows the initial size of the lesion and its infiltration into the liver. The second image illustrates the lack of a clear cleavage plane with the duodenum. The third image highlights the involvement of the hepatic flexure. After 12 months of chemo-immunotherapy, the three images in the right column show marked changes. The first image demonstrates a marked reduction in the lesion size and a notable decrease in the infiltrative component in the liver. The second image highlights the re-establishment of a clear cleavage plane with the duodenum. The third image depicts reduced involvement of the hepatic flexure.

surgery, and ultimately enhance the likelihood of survival (14). A recent study on the use of neoadjuvant chemotherapy for extrahepatic biliary tract cancer, including GBC, concluded that NAT was associated with better overall survival and cancer-specific survival for patients with advanced-stage diseases, without improving survival rates for all surgical patients. This suggests that a tailored approach to NAT is beneficial for certain groups of patients, underscoring the importance of patient-specific treatment plans for enhancing survival outcomes (15). Pathological complete response in advanced GBC is infrequent, only a few case reports described the use of conversion chemotherapy (16).

However, recent advances in chemo-immunotherapy have created new paradigms for treatment. The phase 3 TOPAZ-1 study has been particularly pivotal, demonstrating the benefit of combining durvalumab, an immune checkpoint inhibitor, with gemcitabine and cisplatin (5). This combination not only improved overall survival and progression-free survival but also increased the rates of radiological complete response compared with chemotherapy alone. These findings led to a shift from traditional chemotherapy regimens to more advanced chemo-immunotherapy protocols, where the recent chemo-immunotherapy protocols represent the backbone of first-line treatment in advanced cases. These advancements represent a significant leap forward in the management of GBC, offering new hope for advanced GBC patients with potentially curative responses, especially in settings where only palliative care was previously feasible.

Individual cases and smaller series have reported complete clinical responses in metastatic cholangiocarcinoma patients treated with chemo-immunotherapy. A case utilising pemigatinib, pembrolizumab, and chemotherapy showed a partial response progressing to a complete metabolic response with normalised tumour markers, highlighting the triple therapy's potential effectiveness (7). An approach combining dose-fractioned radiation with PD-1 inhibitors showed significant tumour control and extended survival (8); similarly, a stage IV EBV-associated intrahepatic cholangiocarcinoma patient achieved complete remission with first-line anti-PD-1 immunotherapy and radiotherapy, indicating the potential influence of high PD-L1 expression and other genetic markers on the treatment efficacy (9). Furthermore, another patient reached complete remission with PD-1 inhibitors and paclitaxel, maintaining this state for over two years without relying on established predictive biomarkers for improved efficacy, though mutations in BRCA1, KRAS, and NTRK3 were noted (10).

Several cases of conversion surgery have been reported in GBC (14); however, data on chemo-immunotherapy for advanced diseases following a surgical approach are extremely limited and predominantly consist of case reports (17-19) (Table I).

In 2021, Satyananda *et al* (17) reported on a case that was initially diagnosed as unresectable GBC (cT3N1M0). After cisplatin-gemcitabine chemotherapy and trial-based ipilimumab-nivolumab immunotherapy, a good radiological response and reduction in tumour markers were reported. The patient underwent right portal vein embolisation followed by an open extended right hepatectomy, radical cholecystectomy, and roux-en-Y hepaticojejunostomy reconstruction. Final histology showed a complete tumour response (ypT0N0M0), and the patient was disease-free at the 10-month follow-up.

In 2023, Zhang *et al* (18) reported a case of GBC with jaundice and elevated tumour markers (i.e., CEA, CA 19.9, CA 125, and alpha-fetoprotein). Exploratory laparoscopy with partial cholecystectomy and biopsy revealed stage IV GBC with liver, para-aortic, and retroperitoneal lymph node metastasis. Lenvatinib therapy was started, but a subsequent CT scan showed an increase in tumour mutational burden (TMB). Therapy was shifted to cisplatin-gemcitabine chemotherapy and durvalumab immunotherapy. After three cycles, the tumour marker levels fell to within the normal range and radiographic assessment showed a clinical complete response. The patient underwent residual cholecystectomy and hilar lymph node dissection. Final histology showed a complete tumour response (ypT0N0M0), but the CT scan performed 6 months after surgery revealed an enlargement of the abdominal lymph nodes. SOX regimen and durvalumab were started, and lymph node shrinkage was observed in the subsequent CT scan. The patient was still alive 1 year after the initial diagnosis.

In 2023, Wang *et al* (19) reported a case of metastatic GBC in the liver; the 58-year-old female showed a significant increase in serum β-HCG level (6080.2 IU/l). The patient received chemotherapy with gemcitabine and capecitabine

Table I. Summary of the included studies.

First author/s, year	Sex, age (years)	Reasons for unresectability	CHT	Immunotherapy	PD-L1 status	Other biomarkers	Surgery (resection assessment)	Patient follow-up	(Refs.)
Satyananda *et al*, 2021	M, 59	Stage IIIb	Gemcitabine cisplatin	Ipilimumab nivolumab	NA	NA	Extended right hepatectomy with radical cholecystectomy, lymph node dissection, Roux-Y hepaticojejunostomy (ypT0N0M0)	Disease-free at 10-month follow-up	(17)
Zhang *et al*, 2023	F, 60	Stage IVb	Gemcitabine cisplatin	Lenvanitib durvalumab	+	MSS	Partial cholecistectomy and subsequent completion surgery (residual cholecystectomy and hilar lymph node dissection) (ypT0N0M0)	Alive 1 year after diagnosis	(18)
Wang *et al*, 2023	F, 58	Stage IVb	Gemcitabine capecitabine	Carrellizumab	+	MSS	Radical resection of gallbladder carcinoma and radiofrequency ablation of liver lesions	Disease-free at 14-month follow-up	(19)
Leong *et al*, 2024	M, 39	Stage IVb	Gemcitabine	Durvalumab	NA	NA	Extended right hepatectomy cisplatin and reconstruction with hepaticojejunostomy (ypT1aN0M0)	Disease-free at 6-month follow-up	(20)

CHT, chemotherapy; F, female; M, male; MSS, micro satellite stable; NA, not assessed; PD-L1, programmed death-ligand 1.

plus immunotherapy with carrellizumab. The CT scan after therapy revealed a drastic reduction in the tumour size, and the serum β-HCG level decreased to the normal range. Subsequently, radical resection of gallbladder carcinoma and radiofrequency ablation of liver lesions were performed. Histopathological analysis showed no tumour cells, indicating a pathological complete response. The patient received two more courses of postoperative chemo-immunotherapy and was disease-free at the 14-month follow-up.

In 2024, Leong *et al* (20) reported a case of GBC with jaundice and elevated CA 19.9. The preliminary diagnosis was infiltrative GBC involving the hepatic duct confluence. The patient was a candidate for surgery and underwent right portal vein embolisation. The subsequent CT scan revealed disease progression, and diagnostic laparoscopy confirmed the stage IV GBC. After cisplatin-gemcitabine chemotherapy and durvalumab immunotherapy, the CT scan showed a near complete response, and the patient underwent a laparoscopic extended right hepatectomy with hepaticojejunostomy reconstruction. Final histology confirmed the near complete pathological response (ypT1aN0). Adjuvant gemcitabine, cisplatin, and durvalumab were administered, and the patient was disease-free at the 6-month follow-up.

Complete responses without pathological confirmation are increasingly reported in the literature for cholangiocarcinoma, and similar findings are documented for GBC, although there are only a few cases described (21-23). These findings, particularly those related to the characteristics of long-term responses to immunotherapy, raise questions concerning the role of subsequent surgery and the greater morbidity and mortality associated with extended resections.

In the SWOG 1609 cohort, the combination of anti-CTLA-4 and anti-PD-1 agents led to extended disease control in advanced GBC; one patient (5% of the cohort) achieved a complete response with a median duration of 14.8 months (21). Similarly, Tan *et al* (22) observed a complete response in 10% of the patients treated with PD-1 inhibitors combined with nab-paclitaxel, highlighting the potential of chemo-immunotherapy to facilitate significant tumour regression. Additionally, Rao *et al* (23) reported on the complete response observed at the 11-month follow-up in a patient who initially presented with multiple hepatic metastases from GBC and received radical surgery treated with camrelizumab and apatinib. The relationship between biomarkers, such as PD-L1 expression or TMB, and long-term treatment efficacy remains underexplored in these reports, emphasising the need for targeted research aimed at identifying reliable predictive biomarkers.

The present case harboured an ERBB2 mutation, which is a rare activating point mutation (R678Q) in the juxtamembrane domain (23). Aberrant expression and signalling of the epidermal growth factor receptor family of tyrosine kinases have been implicated in the molecular pathogenesis of cholangiocarcinoma, thereby highlighting the potential efficacy of agents selectively targeting these receptors; extrahepatic BTCs, including GBC, showed a higher HER2 overexpression rate compared with intrahepatic cholangiocarcinoma (24). The mechanisms related to the pathological and physiological responses of GBC to combination therapy are exceedingly complex, involving multiple factors, such as TMB, microsatellite instability, PD-L1 expression, and peripheral blood lymphocyte subpopulations, all contributing to the efficacy of the therapy. Koido *et al* (25) reported that treatment of cholangiocarcinoma cells with gemcitabine resulted in the upregulation of the tumour antigen WT1, calreticulin (an eat-me signal for cells undergoing apoptosis), and PD-L1 but did not establish a direct link with ERBB2 mutations. The patient was PD-L1 negative, which is generally associated with a less likely response to immune checkpoint inhibitors (26). However, a significant response was observed, suggesting that factors beyond PD-L1 status may influence treatment outcomes. ERBB2 mutations, including the rare R678Q mutation found in our patient, have been implicated in various cancers as potential drivers of oncogenesis and targets for therapy (27), although the specific impact of the ERBB2 R678Q mutation on the response to chemo-immunotherapy in GBC remains unclear. The literature does not provide a definitive correlation between this mutation and treatment efficacy. While PD-L1 expression and TMB are commonly evaluated biomarkers, their predictive value is not absolute, and other factors, including specific genetic mutations, may play a role but are not fully understood. Thus, there is justification for combining standard chemotherapy agents with immune checkpoint inhibitors in predominantly microsatellite stable (>97% of BTCs) diseases to support a positive treatment response (17).

In the present study, a complete pathological response was observed in a GBC patient with multiple distant lymphatic metastases and local extension, exhibiting invasion of liver segments 4i and 5, the colonic hepatic flexure, the duodenal bulb, and the pancreatic head. After therapy with gemcitabine, cisplatin, and durvalumab, a significant response to treatment was observed and subsequent surgical resection resulted in a complete pathological response.

In conclusion, first-line chemo-immunotherapy in metastatic cholangiocarcinoma, including GBC, appears to provide promising results, particularly for combinations using newer immunotherapeutic agents. While complete responses are rare, chemo-immunotherapy is associated with significant clinical benefits and may become more common in personalised approaches based on specific tumour characteristics. Further studies are required to refine these therapies and better predict patients who may benefit the most.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

EO, IT, ST, AS, MAP, EA, SV, AR and MG assessed the conception and design of the manuscript, and were involved in acquisition, analysis and interpretation of data. MG, IT and

ST contributed to the investigation and data curation. MAP, EA and AR drafted the article. EO, IT, ST, AS, MAP, EA, SV, AR and MG critically revised the manuscript for important intellectual contents. EO and MG reviewed and edited the final version of the manuscript. EO and MG confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript, and participated sufficiently in the work to take public responsibility for appropriate portions of the content. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The case report did not require approval from a local ethics committee; however, ethical considerations in accordance with the Declaration of Helsinki were adhered to. The patient provided written informed consent.

Patient consent for publication

The patient provided written informed consent for publication of the data and images.

Competing interests

The authors declare that they have no competing interests.

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