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WORD COUNT 3061
TIME SUBMITTED 08-OCT-2023 03:13PM
PAPER ID 103313715

Name of Journal: *World Journal of Gastrointestinal Surgery*
Manuscript NO: 87825
Manuscript Type: CASE REPORT

Systematic sequential therapy for *ex vivo* liver resection and auto-transplantation conversion therapy: A case report and review of literature

auto-transplantation conversion therapy

Abstract

BACKGROUND

Perihilar cholangiocarcinoma (pCCA) is a highly malignancy arising from biliary tree. Radical surgery is the only treatment offering a chance of long-term survival. But limited by tumor's anatomic location and peri-vascular invasion, most patients lose the chance for curative treatment. Therefore, more methods to increase the resectability of tumor as well as improve the outcome are needed.

CASE SUMMARY

A 68-year-old female patient occasionally found a hepatic hilar mass without any obvious symptoms. The laboratory results showed the positive hepatitis B. Magnetic resonance imaging scanning found that the mass (maximum diameter: 41 mm) invaded the main portal vein with left and right branches, as well as middle, left and right hepatic vein, while enlarged lymph nodes were also detected in the hilar. Then the patient was diagnosed with pCCA which the clinical stage was determined as T4N1M0 (Stage IIIC). Considering tumor's anatomic location and vascular invasion, systematic conversion therapy followed by *ex vivo* liver resection and autotransplantation (ELRA) were personalized designed for this patient. Our original systemic sequential therapeutic strategy (lenvatinib and tislelizumab in combination with gemcitabine and cisplatin) was successfully adopted as conversion therapy for her and she achieved partial response

after three cycles of treatment without severe toxicities. Finally, ELRA, anastomotic reconstruction of the middle hepatic vein, the right hepatic vein, the root of portal vein, inferior vena cava and right hepatic artery , and lymph node dissection were performed one month after systemic therapy. Pathological and immunohistochemical examination confirmed a diagnosis of pCCA with lymph node metastasis. Although the middle hepatic vein was partial obstructed four months later, hepatic vein stent implantation solved the problem with success. The patient has survived 22 mo following diagnosis with no evidence of recurrence or metastasis.

CONCLUSION

An effective therapeutic strategy for conversion therapy could greatly increase the feasibility and efficiency of ELRA.

Key Words: perihilar cholangiocarcinoma; *ex vivo* liver resection and auto-transplantation; systemic sequential therapy; conversion therapy; case report

Hu C, Han X, Gao Z, Zhou B, Tang J, Pei X, Lu J, Xu Q, Shen X, Yan S, Ding Y. Systematic sequential therapy for *ex vivo* liver resection and auto-transplantation conversion therapy: a case report. *World J Gastrointest Surg* 2023; In press

Core Tip: Limited by tumor's anatomic location and peri-vascular invasion, most perihilar cholangiocarcinoma patients lose the chance for curative treatment. In this case, we originally put forward systematic conversion therapy followed by *ex vivo* liver resection and autotransplantation (ELRA). The patient achieved partial response after three cycles of systemic sequential treatment without severe toxicities. Soon afterwards, ELRA, anastomotic reconstruction of the middle hepatic vein, the right hepatic vein, the root of portal vein, inferior vena cava and right hepatic artery, and lymph node dissection were performed with success. The patient achieved long time survival and has survived 22 mo following diagnosis with no evidence of recurrence or metastasis.

INTRODUCTION

Originating from biliary tree and/or within the hepatic parenchyma, cholangiocarcinoma (CCA) is a highly lethal, epithelial cell malignancy. CCA predominantly arises from the bile ducts epithelial cells and displays features of cholangiocyte differentiation [1]. According to its anatomic subtype, these heterogeneous cancers can be classified as intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma (pCCA) and distal cholangiocarcinoma (dCCA). pCCA is localized between the second-order bile ducts and the junction of the cystic duct into the common bile duct, dCCA is confined to the common bile duct below the cystic duct insertion, while iCCA is located within the liver parenchyma [2, 3]. Each of the anatomic subtypes is characterized by unique genetic aberrations, clinical presentations and management options.

As the commonest subtype of CCA, pCCA represents more than 50% and radical surgical resection is the only potential treatment offering a chance of long-term survival for the patients with pCCA [4]. But, unfortunately, due to its highly invasive biological characteristics and lack of specific symptoms, most pCCA patients are diagnosed as advanced disease which loses the chances for radical surgery [5]. In addition, extensive hilar invasion, liver involvement and vascular encasement often do preclude curative resection. Therefore, the traditional surgical effect is far from satisfaction and liver transplantation may share as a more promising option for pCCA patients [6].

In 1988, ex vivo liver resection and autotransplantation (ELRA) was firstly introduced by professor Pichlmayr *et al.* as an alternative to liver transplantation for unresectable hepatic tumor [7]. Soon afterwards, ELRA has been constantly developed to improve the resectability of the hepatobiliary malignancies. In 2003, Chui *et al* firstly reported a type IV pCCA patient undergone ELRA, who survived for two years without any sign of tumor recurrence [8]. Nowadays, the rapid development of autologous liver transplantation surgical techniques and vascular reconstruction techniques as well as the application of novel immunosuppressive agents deeply contribute to expand the limits

of resectability and reduce the incidence of chronic allograft rejection, which may greatly benefit the selected patients [9, 10]. However, because of the rigorous admission criteria for patients undergoing liver transplantation, more methods to increase the feasibility of ELRA are needed [11].

Recently, conversion therapy, using systematic therapy and/or non-surgical local therapy to inhibit tumor progression, reduce tumor burden, even reduce TNM staging, provides patients the opportunity to radical surgery and significantly improved the prognosis [1, 12, 13]. In 2021, we firstly reported that an original systemic sequential therapeutic strategy (gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2 on days 1 and 8; lenvatinib 8 mg/day from days 1 to 21; tislelizumab 200 mg on day 15) acquired reliable treatment efficiency on conversion surgery for advanced iCCA patient [14]. Nowadays, here, we presented our new single center experience of this conversion therapy strategy for the treatment of pCCA before ELRA. The prognosis of this 68-year-old female patient was favorable, no evidence of tumor recurrence was found until July 15th, 2023.

CASE PRESENTATION

Chief complaints

A 68-year-old female patient was accidently found a mass in the second hepatic portal region to caudate lobe in local hospital and was admitted to our hospital for further treatment on August 30, 2021.

History of present illness

No special discomfort was complained by this patient.

History of past illness

None.

Personal and family history

None.

Physical examination

No positive signs were showed in physical examination.

Laboratory examinations

No abnormal laboratory results were recorded except alanine aminotransferase (ALT) 43 U/L, aspartate aminotransferase (AST) 46 U/L, anti-HBs (+), anti-HBe (+) and anti-HBc (+).Immunohistochemical staining results were as follows: CK7 (+), CK19 (+), HepPar-1 (-), Arginase-1(-) and Ki-67 labeling index: 40%.

Imaging examinations

B-scan ultrasound showed a hilar mass which leaded to the expansion of intrahepatic bile duct in left lobe of liver. Contrast-enhanced magnetic resonance imaging (MRI) scanning found that the mass (maximum diameter: 41 mm) invaded the main portal vein with left and right branches, as well as middle, left and right hepatic vein (Figure 1. A-D). Enlarged hilar lymph node was also detected by MRI (Figure 1. E). Moreover, there was no invasion of the abdominal aorta or its branches and no filling defect in inferior vena cava according to computed tomography (CT) imaging of abdominal vessels.

FINAL DIAGNOSIS

In general, we made a diagnosis of pCCA with lymph node metastasis. The TNM clinical stage was determined as T4N1M0 (Stage IIIC) according to the American Joint Committee on Cancer (AJCC) staging system, 8th edition.

TREATMENT

After full consideration, the patient lost the chance to surgery and was scheduled for a personalized therapeutic scheme (intravenous gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on day 1, day 8; oral Lenvatinib 8 mg per day from day 1 to day 21; intravenous Tislelizumab 200 mg on day 15). No grade 3/4 treatment-related adverse effect was

detected with three cycles of systemic treatment. Further MRI informed that the mass in hilar was significantly smaller than that in the previous (Figure 1. F-I). The diameter of the largest lesion decreased from 41 mm to 21 mm. According to the standard RECIST 1.1 criteria, the patient successfully achieved partial response (PR) and the lymph nodes in hilar region were also smaller than before (Figure 1. J). Consequently, preoperative multi-disciplinary team carefully reviewed all preoperative results and proposed a surgical strategy for autologous liver segment auto-transplantation.

Surgery was performed in December 1, 2021 and lasted for 740 min. Three-dimensional reconstruction (Figure 3. A) and intraoperative exploration revealed that the tumor invaded the root of left and right hepatic ducts, left and right portal vein, as well as middle and right hepatic vein. First, the left hemi-liver was completely removed *in vivo* and the middle hepatic vein was retained in the right lobe (Figure 3. B). Then, when the right lobe including the tumor was resected (figure 3. C), the right lobe was placed in an ice basin immediately and perfused with 4°C HTK solution. In vitro, the tumor was completed resected and we further used allogeneic iliac vein to lengthen the middle and right hepatic vein respectively. In addition, allogeneic iliac vein was used as the bypass between portal vein and inferior vena cava during the anhepatic phase. Finally, the anastomotic reconstruction of the middle hepatic vein, the right hepatic vein, the root of portal vein, inferior vena cava, and right hepatic artery were performed sequentially (figure 3. D). Moreover, the hepatic portal lymph nodes and para-esophageal lymph nodes were dissected.

OUTCOME AND FOLLOW-UP

The postoperative pathological examination (Figure 2. C, D) showed as follows: the tumor bed with large necrosis area, interstitial fibrosis and tumor residue was 4.0*3.0 cm in size as well as a negative surgical margin; the hepatic portal lymph nodes were 0/3 positive but the para-esophageal lymph nodes were 2/2 positive; moreover, no microvascular and Glisson's capsule invasion were found. The results of immunohistochemical analysis were also as follows: CK7 (+), CK19 (+), HepPar-1 (-),

Arginase-1(-) and Ki-67 Labeling index: 80% (Figure 4). The patient was sent to ICU and extubated at postoperative day 2. Tacrolimus (0.5mg, QD7; 1mg, QD19) was administered to prevent immune rejection and the value of FK506 was closely monitored. Postoperative ultrasound suggested that the maximum blood flow velocity of portal vein, hepatic artery, right hepatic vein and middle hepatic vein were 40.64 cm/s, 70.96 cm/s, 69.02 cm/s and 23.22 cm/s respectively. No severe complications occurred during hospitalization. Therefore, she was successfully discharged at postoperative day 22 with normal liver and heart function.

Two months after surgery, the patient continued to oral capecitabine (1750mg, BID) and lenvatinib (8 mg, QD) as maintenance treatment. At a follow-up of 3 mo, the patient felt subjectively well and no obvious abnormity was found in contrast-enhanced MRI re-examination (Figure 5. A, B). Unfortunately, abdominal enhanced CT indicated the existence of hepatic congestion and hepatomegaly on April 19th, 2022 (Figure 5. C). Meanwhile, the liver function and coagulation function were abnormal, showing as follows: ALT 52 U/L, AST 92 U/L, total bilirubin 40.3 μmol/L, direct bilirubin 17.5 μmol/L, indirect bilirubin 22.8 μmol/L, albumin 32.1 g/L, and serum D-dimer 1040 μg/L. Furthermore, the middle hepatic vein was partial obstructed and the maximum blood flow velocity of portal vein, hepatic artery, right hepatic vein and middle hepatic vein were significantly slower than before. Considering that the thrombus may further impaired liver function, the patient underwent hepatic vein stent implantation on May 5, 2022. After treatment, the liver function returned to normal level. Postoperative ultrasonography indicated that blood flow in the stent is clear and the maximum blood flow velocity of stenting area achieved 118.8cm/s.

One month later, the patient received six cycles targeted therapy and immunotherapy (lenvatinib 8 mg per day from day 1 to day 21; tislelizumab 200 mg at day 15). Further follow-ups showed that no evidence of local recurrence or distant metastasis occurred and hepatic vein stent was good (Figure 5. D). To date, the patient survived well without any severe discomfort more than 22 mo. Figure 6 shows this patient's timeline of initial diagnosis, systemic therapy, surgery, adjuvant therapy and follow-up.

DISCUSSION

Currently, pCCA is one of the most dismal malignancies, which the gold standard curative therapy is radical resection. Disappointingly, less than 50% pCCA patients are eligible for resection [15], and the incidence of R0 resection reported in patients undergoing surgery was only 45% [16]. A need for improvement in tumor resectability and the safety of resection seems therefore obvious. Of note, in contrast to liver resection, liver transplantation is logically an attractive alternative to work out most of problems such as a high potential to leave tumor behind as well as unresectable disease with vascular involvement [6]. ELRA, a unique type of liver transplantation, also provides several benefits. It may improve tumor accessibility so as to achieve a complete tumor resection with clear margins, perform complex vascular reconstruction, reduce ischemic damage to the organ using cold preservation solution, decreased demand for organ donors and reduced immunosuppression compared with allotransplantation [17]. In the past few years, there have been a number of reports related to successful treatment with ELRA [9, 18-21]. Weiner *et al* found relatively favorable outcomes after ELRA in selected patients based on their large collective experience [9]. A systematic review and meta-analysis revealed an R0 resection rate of 93.4% and 1-year survival of 78.4% in cases of ELRA [22]. Besides, one study demonstrated that liver transplantation for pCCA offerred similar or even better outcomes than that for hepatocellular carcinoma or various causes of cirrhosis [23]. Therefore, ELRA may become a more widely accepted and practical treatment option for conventionally unresectable hepatobiliary tumors.

But not all patients are eligible for ELRA. Ideal candidates are those who possess with good functional reserve, tolerate to the procedures, and have a less aggressive malignant tumor [17]. In addition, according to the data from Mayo group, a mass, not larger than 3 cm in diameter, is the selection criteria for pCCA [24]. In our case, the size of malignancy was 4.1 cm in diameter and the tumor located in porta hepatis with middle hepatic vein, portal vein and inferior vena cava involvement. Although ELRA and vascular reconstruction may offer R0 resection and excellent survival, the patient did not

have enough indication. Hence, it was crucial to reduce tumor burden by some effective methods before ELRA so that the patient could acquire more benefits.

Based on our center experience, conversion therapy [25], involving multi-disciplinary systematic treatment preoperatively and aiming to render the tumor more amenable to surgical removal, can be regarded as the more suitable pre-ELRA treatment for this patient. At present, the systematic treatment strategies are various. Over the last decade, the doublet chemotherapy with gemcitabine and cisplatin has been considered the most effective first-line treatment for pCCA, based on the results of ABC-02 trial (NCT00262769) reported in 2010 [26]. But in the new era of targeted therapy and immunotherapy, systemic therapy with molecular and immune therapies has dramatically changed the management of pCCA at advanced stages. Notably, the randomized, double-blind, phase 3 TOPAZ-1 trial (NCT03875235) showed that plus PD-L1 inhibitor durvalumab to gemcitabine and cisplatin significantly improved overall survival (OS) for advanced biliary tract cancer (BTC) compared with gemcitabine and cisplatin alone (median OS: 12.8 mo [95%CI 11.1-14.0] *vs* 11.5 mo [95%CI 10.1-12.5]; hazard ratio [HR] 0.80; two-sided P = 0.021) [27]. Another recent phase 3 clinical trial (KEYNOTE-966; NCT04003636) found that adding pembrolizumab to gemcitabine and cisplatin also remarkably ameliorate OS for advanced BTC (median OS: 12.7 mo [95%CI 11.5-13.6] in the pembrolizumab group *vs* 10.9 mo [95%CI 9.9-11.6] in the placebo group; HR 0.83; one-side P = 0.0034) [28]. Thus, the combination chemotherapy and immunotherapy are safe and effective to patients with pCCA.

Lenvatinib, a multikinase inhibitor that targets vascular endothelial growth factor (VEGF) receptor 1-3, fibroblast growth factor receptors (FGFR) 1-4, platelet-derived growth factor receptor-α (PDGFRα), RET, and KIT, is widely used in many solid tumors, especially in hepatobiliary malignancies [29-33]. Furthermore, more than 50% VEGF overexpression was detected in CCA [34]. By the evidences of the foregoing, we deeply considered whether systematic therapy including chemotherapy, targeted and immunotherapy could make sense for CCA patients. Based on our previous clinical practice, we firstly reported a systemic sequential therapy of gemcitabine, cisplatin,

lenvatinib and tislelizumab could offer great therapeutic effect for preoperative advanced iCCA conversion therapy [14]. Then Zhang *et al* reported a patient with iCCA who first received six cycles of conversion therapy (gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on day 1 and day 8; pembrolizumab, 200 mg every three weeks; lenvatinib 8 mg from day 1 to day 21) that achieved pathologic PR without severe toxicities, followed by radical liver resection, cholecystectomy and hilar lymph node dissection [35]. An attempt of single-arm phase 2 study (NCT03951597) to explore the efficacy and safety of the similar systemic sequential therapy for iCCA were completed in 2022 [36]. The results showed that the objective response rate (ORR) was 80% and the median OS was 22.5 mo (95%CI 15.6-29.3) after the combination therapy of toripalimab, lenvatinib, and gemcitabine plus oxaliplatin for advanced iCCA patients when the median follow-up time was 23.5 mo. In this case, our previous systemic sequential therapy (gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on day 1, day 8; lenvatinib 8 mg from day 1 to day 21; tislelizumab 200 mg on day 15) was successfully treated for the pCCA patient as conversion therapy without any grade 3/4 adverse effect before ELRA and allogeneic vascular reconstruction. The old patients achieved excellent outcome in the end.

CONCLUSION

In conclusion, this is the first case reporting a novel systemic sequential therapeutic strategy followed by ELRA and vascular reconstruction for pCCA. The old female patient achieved PR after the scheduled therapy and no obviously overlap toxicities were occurred during that period. Considering tumor's anatomic location and vascular invasion, ELRA and vascular reconstruction might be a better treatment for her. Finally, tumor was successfully resected *ex vivo* with the negative surgical margin; hepatic vein and inferior vena cava were smoothly reconstructed with allogeneic iliac vein. Herein, this original case did indicate that an effective therapeutic strategy for conversion therapy could greatly increase the feasibility and efficiency of ELRA and vascular reconstruction. Nowadays, our phase 2 clinical trial (NCT05532059), designed to explore the efficacy and

safety of this systemic therapy for CCA patients, is ongoing and hope to give more beneficial treatment options for advanced CCA.

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