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Successful treatment of stage IIIB intrahepatic cholangiocarcinoma using neoadjuvant therapy with the PD-1 inhibitor camrelizumab: A case report

Zhu SG *et al*. Successful Treatment of ICC on stage IIIb

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Abstract

BACKGROUND

The prognosis of intraclass correlation coefficient (ICC) with lymph node metastasis is poor. The feasibility of surgery is not certain, which is a contraindication according to National Comprehensive Cancer Network guidelines. The role of immunotherapy as a neoadjuvant therapy for ICC is not clear. We describe a case of ICC with lymph node metastasis that was successfully treated with neoadjuvant therapy.

CASE SUMMARY

A 60-year-old male with a liver tumor was admitted to our hospital. Enhanced computed tomography and magnetic resonance imaging revealed a space-occupying lesion in the right lobe of the liver. Multiple subfoci were found around the tumor, and the right posterior branch of the portal vein was invaded. Liver biopsy indicated poorly differentiated cholangiocytes. According to the American Joint Committee on Cancer disease stage classification, intrahepatic cholangiocarcinoma with hilar lymph node metastasis (stage IIIB) and para-aortic lymph node metastasis were suspected. A current report showed that two patients with stage IIIB ICC achieved complete response (CR)

13 mo and 16 mo after chemotherapy with a PD-1 monoclonal antibody. After multidisciplinary consultation, the patient was given neoadjuvant therapy, surgical resection and lymph node dissection, and postoperative adjuvant therapy. After three rounds of PD-1 immunotherapy (camrelizumab) and two rounds of GP regimen chemotherapy (gemcitabine combined with cisplatin), the tumor size was reduced. Therefore, a partial response was achieved. Exploratory laparotomy found that the lymph nodes of Group 16 were negative, and the tumor could be surgically removed. Therefore, the patient underwent right hemihepatectomy plus lymph node dissection. The patient received six rounds of chemotherapy and five rounds of PD-1 treatment postoperatively. After 8 mo of follow-up, no recurrence was found, and CR was achieved.

CONCLUSION

Neoadjuvant therapy combined with surgical resection is useful for advanced-stage intrahepatic cholangiocarcinoma. This report is the first successful treatment of stage IIIB intrahepatic cholangiocarcinoma after neoadjuvant therapy with a PD-1 inhibitor.

Key Words: Intrahepatic Cholangiocarcinoma; Lymph Node Metastasis; Neoadjuvant Therapy; Immunotherapy; Chemotherapy; Surgical Resection; Case report

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Core Tip: At present, the objective remission rate of intraclass correlation coefficient (ICC) in the treatment of advanced hepatocellular carcinoma (HCC) patients is approximately 20%. The development of more sensitive and efficient predictive methods will improve the benefits of ICC therapy in potential patients with advanced HCC and benefit patients who are suitable for ICC therapy. This will hopefully open up

a new prospect of immunotherapy for liver tumors. Immunotherapy may be a potential treatment option for hepatic ICC.

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is an adenocarcinoma originating from the secondary bile duct and its branch epithelium. ICC accounts for approximately 10%-15% of primary liver cancers[1]. ICC is the primary malignant tumor of the liver after hepatocellular carcinoma (HCC)[2]. The incidence rate has increased in recent years. The exact cause of intrahepatic cholangiocarcinoma is not clear. The well-known risk factors for ICC include congenital choledochal cysts, chronic cholangitis, chronic inflammatory bowel disease, primary sclerosing cholangitis, parasitic infection, chemical carcinogens (such as thorium dioxide and nitrosamine), genetic factors, biliary cirrhosis, cholelithiasis, alcoholic liver disease and nonspecific cirrhosis. Hepatitis viruses are also closely related to ICC[3]. The general morphology of ICC is divided into three types: mass type, peritubular infiltration type and intratubular growth type. The most common type is the mass type, which accounts for 60% to 80% of ICCs. The periductal infiltration type accounts for 15% to 35%. This type may have diffuse infiltration along the biliary system and portal vein system, which results in bile duct stenosis and peripheral bile duct dilatation. The intraductal growth type accounts for 8% to 29%. This type mostly shows papillary, polypoid or granular growth that spreads along the superficial bile duct[4]. We report the case of a patient with advanced ICC who was successfully treated with neoadjuvant therapy combined with surgical resection.

CASE PRESENTATION

Chief complaints

Right upper abdominal pain for 1 wk.

History of present illness

A 60 years old male, 1 wk ago was no obvious cause of right upper abdominal pain, it's persistent dull pain, no radiating pain, no fatigue, poor appetite, fearless cold and fever. He visited the local hospital outpatient department, and upper abdominal computed tomography (CT) examination suggested liver space occupying lesions. Since the onset of the disease, his spirit, sleep and diet are a little poor, and his urine and feces are normal. He has lost 7.5 kg in weight in the past 2 mo.

History of past illness

He has a history of hepatitis B for 30 years and is currently receiving oral entecavir antiviral therapy. Nothing else special.

Personal and family history

No smoking or drinking history, family members are healthy.

Physical examination

The abdomen is soft, without tenderness and rebound pain. The liver can be touched 2 cm below the right costal, the spleen can be touched 3 cm below the left costal. There is percussion pain in the liver area, and there is no other special pain.

Laboratory examinations

CA19-9 is 1844 U/mL, hepatitis B virus deoxyribonucleic acid is 6.0e2 IU/mL. Carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP) and liver function are normal.

Imaging examinations

Computed tomography and Magnetic resonance imaging showed that the tumors were located in the right lobe, the longest diameter is about 20 cm; hilar lymph node metastasis was found (Fig. 1).

FINAL DIAGNOSIS

ICC (stage IIIB) was initially diagnosed with hilar and retroperitoneal lymph node metastasis.

TREATMENT

We performed liver biopsy, and the pathological results showed poorly differentiated cholangiocarcinoma (Fig. 2). After multidisciplinary consultation, we determined that the patient should be given neoadjuvant therapy, surgical resection and lymph node dissection, and postoperative adjuvant therapy (Fig. 3).

OUTCOME AND FOLLOW-UP

CT imaging found no recurrence after 8 mo of follow-up, and CA199 decreased from 1844 U/mL to 4.76 U/mL. An oncology assessment determined a prorenin status (Fig. 4).

DISCUSSION

Intrahepatic cholangiocarcinoma has high malignancy, a poor prognosis and few long-term survivors. The prognosis of patients without surgery is very poor, and the 3-year survival rate is only 40% - 50% after surgery[5]. Compared to other liver malignancies, ICC has a shorter survival time and lower resection and cure rates[6]. The gross classification of ICC is related to tumor prognosis. The prognosis of the peritubular infiltration type is the worst, followed by the mass type. The intratubular growth type has the best prognosis. Tumor markers lack sensitivity and specificity for the diagnosis of ICC. CA19-9 is valuable in the diagnosis of tumors, the evaluation of tumor resection and prognosis prediction. However, CEA, AFP and CA-125 are less valuable in the diagnosis of ICC[7]. The definite diagnosis depends on the combination of imaging and pathological examination[8]. Intrahepatic cholangiocarcinoma is more likely to recur than hepatocellular carcinoma[9]. The survival of patients with ICC is affected by the number of tumors, the extent of liver resection, the degree of tumor differentiation and

the type of tumor cells. According to the National Comprehensive Cancer Network (NCCN) guidelines, preoperative biopsy is not necessary, especially in surgically resectable cases. Imaging results indicating suspicious nodules should be treated as malignant, and diagnostic laparoscopic exploration is recommended to exclude unresectable disseminated lesions[10]. Exploration and evaluation should include examinations for multiple intrahepatic cancers, lymph node metastasis and distant metastasis. Lymph node metastasis and distant metastasis outside the portal hepatis should be considered surgical contraindications. Hilar lymph node dissection should be performed routinely to provide staging and prognosis information. According to the NCCN guidelines, radical surgery (plus lymph node dissection) is the only curative treatment[11]. Surgical indications and neoadjuvant therapy remain the focus of clinical judgments[12]. One study reported two patients with stage IIIB ICC achieved CR 13 mo and 16 mo after chemotherapy with PD-1 monoclonal antibody[13]. For the present case of intrahepatic cholangiocarcinoma with hilar lymph node metastasis, abdominal aortic lymph node metastasis was suspected and was classified as American Joint Committee on Cancer stage IIIB. Multidisciplinary discussion determined that the patient should receive neoadjuvant therapy, surgical resection and lymph node dissection, and postoperative adjuvant therapy. Neoadjuvant therapy included chemotherapy and immunotherapy. After immunotherapy with a PD-1 inhibitor and chemotherapy with the GP regimen, a re-evaluation showed that the tumor had shrunk and was necrotic. An oncology evaluation determined a PR status (Fig. 5). According to the NCCN guidelines, the patient continued to receive immunotherapy and chemotherapy after tumor resection, and no recurrences were found. Lymph node dissection is another focus of clinical debate. The existing research shows that extended dissection does not improve the prognosis. However, the NCCN and European Society of Medical Oncology guidelines recommend routine hilar lymph node dissection. The NCCN guidelines consider positive extrahepatic lymph node metastasis as a surgical contraindication and recommend neoadjuvant therapy followed by surgery at a lower stage. Therefore, the independent risk factors for the prognosis of the patient included a

less than 1-cm distance between the cutting edge and the tumor, a tumor diameter greater than 5 cm, multiple tumors, microvascular invasion, and positive pathological lymph node metastasis[12,14]. A previous study confirmed that lymph node dissection did not improve the prognosis of patients with intrahepatic cholangiocarcinoma[15]. Postoperative pathology confirmed that positive lymph node metastasis is an independent risk factor affecting the prognosis of patients with intrahepatic cholangiocarcinoma. This relationship confirms the clinical value of lymph node dissection and shows that lymph node dissection remains associated with many problems[15]. Lymph node dissection is routine, and the Chinese Society of Clinical Oncology biliary system tumor diagnosis and treatment expert consensus 2019 recommend active surgical resection and lymph node dissection. Therefore, there is no consensus on the scope of regional lymph node dissection[14]. We should carefully consider extended hepatectomy, the improvement of chemotherapy, and the emergence of immunotherapy and radiotherapy. With the development of surgery, adjuvant therapy has become an important means to improve the prognosis of intrahepatic cholangiocarcinoma[16,17]. Another point of contention about ICC is the absence of randomised controlled trial studies on preoperative neoadjuvant therapy for ICC. A multicenter study of 62 cases of ICC with neoadjuvant chemotherapy had a median OS of 47 mo after resection, and 74 cases of unresectable ICC had a median OS of 24 mo after 6 cycles of chemotherapy[18]. Preoperative neoadjuvant therapy is a "TEST" because there are no reports of immunotherapy as neoadjuvant or transformation therapy.

CONCLUSION

Immunotherapy is a current research hotspot. PD-1 inhibitors are effective for solid tumors, but only melanoma and lung cancer are clinical indications for immunotherapy. The objective remission rate of ICC in the treatment of advanced HCC patients is approximately 20%, which shows a certain efficacy, but more phase III clinical trials are needed for verification. The development of more sensitive and

efficient predictive methods will improve the benefits of ICC therapy in potential patients with advanced HCC and benefit patients who are suitable for ICC therapy. These improvements will hopefully open a new prospect of immunotherapy for liver tumors[19]. Immunotherapy may be a treatment option for hepatic ICC, but it must be confirmed by a larger sample of cases[20]. Its role in preoperative neoadjuvant therapy for intrahepatic cholangiocarcinoma is a hot topic in clinical trials[21]. Overall, the value of neoadjuvant therapy, the time of surgery after neoadjuvant therapy, the necessity of lymph node dissection, the means of adjuvant therapy, and the treatment plan after recurrence remain hot topics of current research.

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