The Multidisciplinary Treatment of Advanced Gallbladder Cancer to Disease-Free Survival: A Case Report

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Abstract

Background: Gallbladder cancer is the most common malignant tumor in the biliary system and is characterized by strong aggressiveness and an extremely poor prognosis. Current treatment for advanced gallbladder cancer remains unsatisfactory. Here we reported a patient with stage IV gallbladder cancer who achieved disease-free survival by multidisciplinary treatment.

Case presentation: A 73-year-old man presented to our hospital with right abdominal pain for 3 days and was diagnosed with advanced gallbladder cancer with multiple intrahepatic metastases and distant lymph node metastases. The patient initially received chemotherapy, targeted therapy, radioactive seed implantation, and immunotherapy as there was no specific indications for radical surgery. With the progression of these adjuvant therapies, the patient's tumor makers gradually decreased but remained higher than normal, lymph node metastases gradually disappeared, and intrahepatic metastases were gradually limited to the left liver. Finally, the patient received a radical surgery of left hepatectomy with partial diaphragmatic resection and radical lymphadenectomy. To date, the patient has survived for more than six years post-treatment, and the level of tumor markers is normal and the imaging examination shows no signs of disease recurrence.

Conclusion: The treatment of advanced gallbladder cancer remains pessimistic in the current medical arena. This successful case is an inspiration and we believe that multidisciplinary treatment can benefit patients with advanced gallbladder cancer and help them achieve long-term survival or even disease-free survival.

Introduction

Gallbladder cancer is the most common malignant tumor in the biliary system, and the global average incidence rate of gallbladder cancer is approximately 2.71/100000 [1]. The prognosis of gallbladder cancer is extremely poor, and radical surgery is the only way to cure gallbladder cancer. However, the onset of gallbladder cancer is insidious and difficult to diagnose at an early stage. Many patients are accidentally discovered or already in the advanced stage when discovered, thereby losing the opportunity of radical surgery. With the development of adjuvant therapy such as chemotherapy, radiotherapy, targeted therapy, and immunotherapy, many studies have proven that preoperative adjuvant therapy can increase the resectability and survival time of advanced malignancies [2]. Here, we reported a patient with stage IV gallbladder cancer who has survived for more than six years and is currently in disease-free survival after multidisciplinary treatment.

Case Presentation

On December 07, 2014, a 73-year-old man presented to our hospital with right abdominal pain for 3 days. On physical examination, he presented with mild tenderness in the right upper quadrant of the abdomen and positive for Murphy's sign. The patient had no family history of cancer. Tumor markers showed

alpha-fetoprotein (AFP), 1.61 IU/L (normal, 0-5.8 IU/L); carcinoembryonic antigen (CEA), 115.8 IU/ml (normal, 0-5 ng/ml); carbohydrate antigen19-9 (CA19-9), > 1000 IU/ml (normal, 0-27 IU/L); CA12-5, 112.3 IU/ml (normal, 0-35 IU/L). Abdominal magnetic resonance imaging (MRI) indicated that gallbladder cancer with multiple hepatic metastases and peritoneal metastases (Fig. 1). ^{18}F -FDG PET/CT showed that gallbladder cancer with multiple hepatic metastases, the invasion of adjacent peritoneum, and multiple lymph node metastases of the right supraclavicular fossa, the right inner mammary area, the right frontal portion of diaphragm, and the peri pancreas (Fig. 2). Subsequently, the patient underwent a fine needle aspiration biopsy of the intrahepatic metastases and the pathological examination indicated adenocarcinoma (Fig. 3).

Based on all the above examinations, the patient was diagnosed with stage IV gallbladder cancer with multiple intrahepatic metastases and multiple lymph node metastases. We recommended that the patient initially went to the oncology department to receive adjuvant treatment. On March 25, 2015, the patient started receiving 7 cycles of chemotherapy of gemcitabine and oxaliplatin (GEMOX) and started receiving targeted therapy of cetuximab from the second cycle of chemotherapy. During the chemotherapy and targeted therapy, the patient suffered from biliary hemorrhage, and it was cured by arterial angiography and arterial embolization. The level of tumor markers gradually decreased during chemotherapy and targeted therapy (Fig. 4). After seven cycles of chemotherapy on August 6, 2015, abdominal MRI showed the malformation of the gallbladder, thickening of the cystic duct and common bile duct wall, and multiple intrahepatic metastases and the largest metastasis was approximately 37 mm $\times$ 56 mm in size and located in the right liver (Fig. 5).

In October 2015, the patient underwent radioactive seed implantation in an outside hospital for further treatment. On January 2, 2016, the patient started receiving continuous immunotherapy of programmed death 1 (PD-1) inhibitor nivolumab and targeted therapy of cetuximab and apatinib. Due to the side effects of hypertension, apatinib was in turn replaced with nintedanib and regorafenib. On March 18, 2016, ^{18}F -FDG PET/CT depicted: (1) some intrahepatic lesions were larger than the previous scans, and new lesions appeared in the left liver with increased ^{18}F -FDG uptake; (2) some lesions of gallbladder were smaller than before; (3) lymph node metastases of the right supraclavicular fossa, the right inner mammary area and peri pancreas disappeared.

On February 06, 2018, the level of the patient's tumor markers was CEA, 82.84 ng/ml; CA19-9, 54.60 IU/ml; CA12-5, 391.40 IU/ml. Abdominal computed tomography (CT) indicated an unclear gallbladder display, a left hepatic metastasis approximately 84 mm $\times$ 59 mm in size, and multiple liver cysts (Fig. 6). ^{18}F -FDG PET/CT showed that a left hepatic metastasis approximately 92 mm $\times$ 60 mm in size, and the right hepatic metastasis was significantly smaller than before (Fig. 7). Since the distant lymph node metastasis had disappeared and the metastasis was mainly limited to the left liver, the patient was subsequently treated with radical surgery of left hepatectomy with partial diaphragmatic resection and radical lymphadenectomy (Fig. 8). We did not find the gallbladder in the surgical specimens, and we considered the gallbladder might have gradually disappeared during the adjuvant treatment. The postoperative pathological examination confirmed a moderately poorly differentiated

cholangiocarcinoma of 90 mm $\times$ 60 mm $\times$ 60 mm in size in the left liver, perineural invasion, liver capsule invasion, diaphragm invasion, and negative for the liver resection margin. The postoperative immunohistochemical examination indicated ARGINASE-1 (-), CK19 (+), GPC-3 (partial +), hep-par (-), CEA (partial+), CK20 (-), CK7 (+) (Fig. 9).

Postoperatively, the patient still received regular immunotherapy therapy and targeted therapy. On October 24, 2019, the patient came to our hospital for a follow-up, the tumor markers have reversed to normal levels with CEA, 2.23 ng/ml; CA19-9, 21.45 IU/ml; CA12-5, 11.54 IU/ml. Abdominal CT showed no signs of tumor recurrence (Fig. 10). On June 12, 2020, the patient's tumor markers remained in normal levels with CEA, 1.74 ng/ml; CA19-9, 22.32 IU/ml; CA12-5, 10.79 IU/ml. The patient's entire treatment process from being diagnosed with gallbladder cancer to the final surgery is shown (Fig. 11).

This study was approved by the Institutional Review Board of the First Affiliated Hospital of Dalian Medical University. Written informative consent was signed by this patient.

Discussion

The prognosis of advanced gallbladder cancer is extremely poor and the 5-year survival rate for stage III, IVA, and IVB are only 29%, 12.4%, and 2.5% respectively [3]. Meanwhile, the treatment for advanced gallbladder cancer is still controversial. Many clinicians and even experienced surgeons are confused and pessimistic about the treatment of advanced gallbladder cancer [4]. With the development of adjuvant therapy, multidisciplinary treatment was a promising approach for advanced malignancies. We reported a patient with advanced gallbladder cancer who was cured by chemotherapy, targeted therapy, radioactive seed implantation, immunotherapy, and radical surgery.

Chemotherapy is a very important treatment for patients with advanced cancer. A Phase III randomized controlled multicenter trial [5] founded that compared with the gemcitabine only group, the cisplatin plus gemcitabine group could increase the survival from 1 month to 4 months if cisplatin plus gemcitabine is given as the first-line treatment for advanced biliary tract cancer (BTC). A meta-analysis [6] including two randomized trials also showed cisplatin plus gemcitabine could significantly improve progression-free survival (PFS) and overall survival (OS) for advanced BTC regardless of ethnicity.

Cetuximab is a targeted therapy against epithelial growth factor receptor (EGFR) and can improve the prognosis of various malignant tumors. A phase 2 study [7] involving 30 patients with unresectable advanced or metastatic biliary tract cancer found that cetuximab plus gemcitabine and oxaliplatin (GEMOX) were well tolerated and had obvious anti-tumor activity, and nine patients underwent a potential radical secondary resection after a major response to treatment. However, a randomized, open-label, non-comparative phase 2 trial [8] found out that compared with chemotherapy alone, cetuximab plus GEMOX in patients with advanced biliary tract tumors did not show a survival advantage. Recently, a systematic review and meta-analysis [9] showed the addition of anti-EGFR monoclonal antibodies to the gemcitabine-based first-line did not significantly improve the OS and PFS, nor the objective response rate of patients with advanced BTC. Whether cetuximab can or cannot benefit patients with advanced BTC is

still a topic that is under research and we are hoping for a high-quality result that would benefit the future of the medical and surgical fields. The level of our patient's tumor markers gradually decreased during chemotherapy and targeted therapy, which indicated that chemotherapy and targeted therapy were helpful for the patient.

After seven cycles of adjuvant chemotherapy, our patient was treated with radioactive seed implantation and immunotherapy in turn. Radioactive seed implantation can provide continuous therapeutic doses in the tumor target area and rapidly decrease the distance of seeding, thereby causing tumor cell death and delaying tumor growth, and only causing minor injury to normal tissues [10, 11]. Cancer cells can evade immune surveillance through molecular interactions of immune checkpoint proteins, including programmed death 1 (PD-1), PD-ligand-1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Immunotherapy based on checkpoint blockers can block the inhibitory pathways of T-cell activation, thereby enabling tumor-reactive T cells to recognize tumor antigens and restore the antitumor immune response [12]. Although immunotherapy has been proven to benefit patients with advanced cancer such as non-small cell lung cancer, urothelial carcinoma, hepatocellular carcinoma, melanoma, and renal cell carcinoma, the efficacy of immunotherapy for advanced BTC is still unclear [13]. With the progression of radioactive seed implantation and immunotherapy, our patient's lymph node metastases gradually disappeared and intrahepatic metastasis was gradually limited to the left liver. Therefore, we believed that radioactive seed implantation and immunotherapy did benefit our patient and increased the resectability. We also look forward to future more studies on immunotherapy for BTC.

Conclusion

We reported a patient with stage IV gallbladder cancer who was cured by multidisciplinary treatment, we believed that the chemotherapy, targeted therapy, radioactive seed implantation, and immunotherapy were beneficial to our patient and helped him acquire the chance for radical surgery. This successful case can provide an effective evidence for the future multidisciplinary treatment of advanced gallbladder cancer, and more successful cases and studies are necessary in the future.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare no conflict of interest.

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Author contributions

BZ, SL and ZL wrote and corrected the manuscript; KP and LS reviewed and corrected the manuscript; ML, PL, DS and WB were the patient's surgeon; WB and DS supervised and edited the manuscript; all authors approved the final version of the manuscript.

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Figures

Figure 1

Abdominal MRI of the patient’s first admission on December 07, 2014.

Figure 2

18F-FDG PET/CT of the patient’s first admission on December 07, 2014.

Figure 3

Pathology of fine needle aspiration biopsy with intrahepatic metastases.

The level of tumor markers

Figure 4

The level of tumor markers during chemotherapy and targeted therapy.

Figure 5

Abdominal MRI after seven cycles of chemotherapy on August 6, 2015.

Figure 6

Abdominal CT before surgery on February 06, 2018.

Figure 7

^{18}F -FDG PET/CT before surgery on February 06, 2018.

Figure 8

A specimen removed from the operation.

Figure 9
 Postoperative pathological and immunohistochemical examination.

Figure 10
 Abdominal CT of postoperative follow-up.

Figure 11

The entire course of the patient from the first admission to the post-operative follow-up.

Supplementary Files

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