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Case Report

Banxia Xiexin Decoction (半夏泻心汤) Combined with Afatinib in Treatment of Advanced Gallbladder Cancer: Case Report and Literature Review

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Gallbladder cancer (GBC) is a malignancy of biliary tract which is infrequent in developed countries but common in some specific geographical regions of developing countries.[1] Currently, GBC has a low early diagnosis rate and an extremely poor prognosis, leading to major problems for treatment of GBC. Liver invasion and metastasis one of the main causes of its poor prognosis, with its average overall survival of 6 months, and a 5-year survival rate of 5%.[2] Advanced GBC is still lack of effective treatment programs. High-lethal GBC is in urgent need of an effective treatment plan. So far, the standard first-line treatment for advanced GBC is systemic chemotherapy with gemcitabine and cisplatin, and there are no standard second- and third-line treatments for patients with GBC.[3] With the development of molecular biology technology, the gene profiles of various tumors are constantly being improved, and targeted drugs have been tried in various tumor treatments, and have achieved good results, at the same time, the adverse reactions of targeted drugs are gradually being paid attention to.[4] In recent years, with the in-depth study of Chinese medicine (CM) in the field of cancer treatment, it is found that CM can alleviate the adverse reactions of targeted drugs, and the quality of life of patients with advanced malignant tumors has been improved.[5,6] Therefore, CM combined with targeted therapy might be a better choice for patients with advanced GBC.

Case Report

A 55-year-old female patient sought medical attention in February 2017 for abdominal pain. Chest and abdomen computed tomography (CT) revealed a mass of abnormally high metabolism in the region of the gallbladder and multiple soft tissue nodules in the liver parenchyma and hilar area. The initial diagnosis was GBC, with the addition of liver parenchyma and hilar as secondary malignant tumors. The patient underwent cholecystectomy plus partial liver resection and hepatic lymphadenectomy in Renji Hospital, Shanghai Jiao Tong University School of Medicine, China. Surgical pathology confirmed poorly differentiated adenocarcinoma from the gallbladder, poorly differentiated carcinoma infiltration and metastasis in liver areas, and lymph node metastases (4/5, Appendix 1). Immunohistochemistry staining were positive for human epidermal growth factor receptor-2 (HER2) and c-Met proto-oncogene (100% ++) and negative for anaplastic lymphoma kinase. Gene amplification with fluorescence in situ hybridization confirmed highHER2 levels (Appendix 2A) and low epidermal growth factor receptor (EGFR) levels (Appendix 2B). The cancer antigen 19-9 (CA 19-9) level was 664 U/mL (normal range, 0–39 U/mL).

One and a half months after surgery, the patient developed jaundice. Magnetic resonance imaging (MRI) showed that liver lesions and hilar metastatic lymph nodes were increased compared with the previous diagnosis, the common bile duct was infiltrated by the tumor and the intrahepatic bile duct was significantly expanded. The patient underwent 2 additional surgeries, percutaneous transhepatic cholangial drainage and biliary stent placement. One week later, jaundice gradually disappeared (Figure 1A). The patient's CA 19-9 decreased to 190 U/mL. She began receiving systemic chemotherapy with gemcitabine [1.0 g/m^2, intravenously guttae (ivgtt), day 1, 8] combined with

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oxaliplatin (130 mg/m^2, ivgtt, day 2) from April 2017 through to June 2017. The result was progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1, Figure 1B), the patient's CA 19-9 increased to 210 U/mL. Subsequently, the second-line treatment was applied with trastuzumab (6 mg/kg, ivgtt, day 0), paclitaxel (130 mg/m^2, ivgtt, day 1) and capecitabine (1250 mg/m^2, twice daily, day 1–14) from June 2017 through to July 2017 (Figure 1C). Because of multiple chemotherapy, the patient's physical state declined significantly, CA 19-9 increasing to 232 U/mL. Then the patient was admitted to our Integrative Medicine Cancer Center at the First Affiliated Hospital of Anhui Medical University, where she started the third-line treatment with afatinib (40 mg, once daily) from July 17, 2017. MRI scan showed favorable outcomes after taking afatinib for 27 days, the assessment result is partial response, closed to complete reponse state (Figure 1D). The patient developed diarrhea on the 4th day after taking afatinib, 6 times a day. Oral anti-diarrhea drugs such as loperamide hydrochloride capsules and montmorillonite powder were used. The main manifestations of the patient were frequent belching, bloating, anorexia, fatigue, limb weakness, diarrhea and oliguria, with greasy and slightly hellowish tongue-fur, and deep, string pulse. According to our experience in the treatment of drug-induced diarrhea,[7] Banxia Xiexin Decoction (半夏泻心汤, BXD; composed of *Rhizoma pinelliae* 12 g, *Radix scutellariae* 9 g, *Rhizoma zingiberis* 9 g, *Rhizoma coptidis* 3 g, *Fructus jujubae* 9 g, *Radix ginseng* 9 g, and *Radix glycyrrhizae* 9 g) was used to treat afatinib-associated diarrhea since July 20, 2017. The patient's symptoms of diarrhea and bloating were significantly relieved. Flow chart of treatment is shown in Figure 2.

Beginning on August 10, 2017, the patient entered the follow-up period, checked once every 2 months. The CA 19-9 level had decreased to normal. Until December 16, 2017, the evaluation results were the stable disease (SD). However, on January 15, 2018, The patient developed a mild right abdomen pain. MRI showed that new lesions appeared again in the right lobe of the liver (Figure 3). The CA 19-9 level was higher than normal (Figure 4). When the evaluation result came out as PD, the patient immediately stopped taking BXD and afatinib. No tumor metastases were found in the patient's head MRI, chest CT, and whole body bone scans. During the treatment of BXD and afatinib, she only had a mild rash and did not experience diarrhea again, at the same

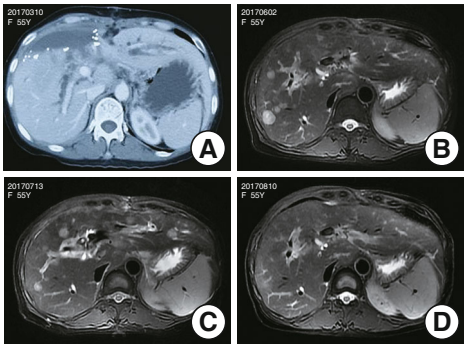

Figure 1. Patient's CT and MRI Pictures

Notes: CT: computed tomography; MRI: magnetic resonance imaging. A: CT picture of the patient before chemotherapy (March 2, 2017). B: After 2 cycles of gemcitabine chemotherapy, magnetic resonance imaging (June 2, 2017) showed that liver metastases rapidly increased. C: After patients underwent 2 cycles of "Herceptin" and "paclitaxel + capecitabine" chemotherapy, and magnetic resonance imaging (July 13, 2017) showed that the number of lesions slightly reduced than before, but some lesions significantly increased. Overall assessment showed that the patient's condition was progressing. D: After Banxia Xiexin Decoction and afatinib (40 mg/d) treatment for 27 days, magnetic resonance imaging (August 10, 2017) showed the volume of intrahepatic lesions was significantly reduced, the number of intrahepatic lesions was decreased.

time, the patient's Eastern Cooperative Oncology Group (ECOG) performance status was 1–2. Bone marrow test showed hemoglobin, white blood cells, neutrophils and platelets were normal; liver aspartate aminotransferase and alanine aminotransferase were less than or equal to twice the upper normal limit. The patient's progression-free survival (PFS) was 183 days.

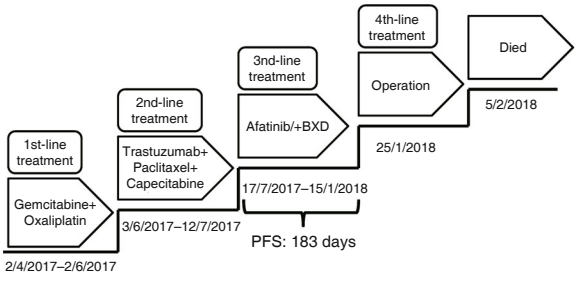

Figure 2. Flow Chart of Patient's Treatment

Notes: BXD: Banxia Xiexin Decoction; PFS: progression free survival. The patient started receiving monotherapy with afatinib on July 17, 2017, and began receiving BXD in combination with afatinib on July 20, 2017.

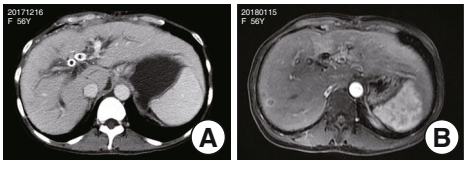

Figure 3. Imaging Pictures after 5- and 6-Month Treatments of Banxia Xiexin Decoction and Afatinib

Notes: A: CT imaging (December 16, 2017) shows that liver lesions have basically disappeared; B: magnetic resonance imaging (January 15, 2018) showed new lesions in the right lobe of the patient's liver.

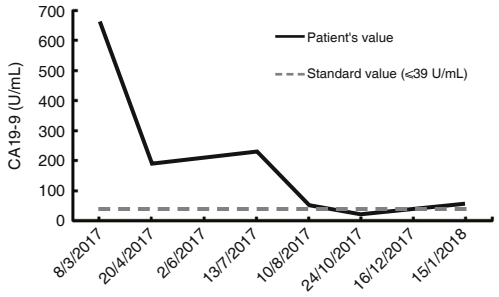

Figure 4. Change of Patient's Cancer Antigen 19-9

On January 25, 2018, under her own strong request, the patient underwent a tumor resection at the Second People's Hospital of Hefei, Anhui Province, China. After the operation, abdominal infection occurred. Eventually, the patient died of septic shock on February 5, 2018 due to ineffective anti-infective treatment. The patient's overall survival was 360 days.

Discussion

In recent years, the incidence of GBC has shown an upward trend in China, GBC was more prone to occur in elderly women.[8] Improving the survival rate of patients with advanced GBC is an urgent issue to be solved in clinical practice.

The patient had undergone two surgical treatments and her condition was not controlled. In the treatment of advanced GBC, conservative treatment is the only available treatment. Chemotherapy and Chinese herbal medicine are now treatment options for advanced GBC.

Previous study has shown that the efficacy of first-line chemotherapy regimens based on gemcitabine are 10% to 40%.[9] Three types of chemotherapy drugs were used: gemcitabine, fluoropyrimidine and platinum compounds.[10] However, the patient received a gemcitabine-based chemotherapy regimen and her condition was not controlled. There is no clear and effective solution for the second- and third-line chemotherapy of advanced GBC.

It has been reported that trastuzumab binds effectively to conventional cytotoxic drugs, including gemcitabine and cisplatin, the standard first-line therapy treatment option for biliary tract cancers (BTC) patients.[11,12] A case reported a patient with biopsy proven HER2 positive metastatic GBC, who had received combinations of gemcitabine with cisplatin, capecitabine and oxaliplatin prior to this line of treatment, experienced a dramatic response to trastuzumab and paclitaxel after 9 weeks of therapy.[13] Therefore, HER2 testing is still of great significance to the progression of GBC patients, despite the traditional treatment options.[14] In this case, gemcitabine and oxaliplatin were used as a first-line treatment, but with negative results. Second-line treatment was the combination of trastuzumab, paclitaxel and capecitabine; however the patient physically declined and clinical efficacy was poor.

At present, studies on GBC-related signaling pathways mainly focus on the ErbB, Angiogenesis, Hedgehog, Notch, PI3K/AKT/mTOR, MAPK/ERK, and Wnt pathways. The ErbB family includes four tyrosine kinase receptors, HER1 (ErbB1, EGFR), HER2 (ErbB2, NEU), HER3 (ErbB3), and HER4 (ErbB4). The role of ErbB protein in GBC cells confirmed that this family of proteins can promote GBC cell proliferation and invasion, suggesting that it plays an important role in the pathogenesis of GBC.[15] Afatinib has the same HER-2 target as Herceptin, but is also the first irreversible ErbB family blocker. Afatinib can block EGFR, HER2 and ErbB4 by covalently binding irreversibly. As ErbB3 does not have a kinase domain, it cannot be directly blocked by afatinib; however, afatinib was found to prevent ligand-dependent phosphorylation of ErbB3 in clinical studies.[16] One study showed 2 new HER2-amplified BTC cell lines SNU-2670 and SNU-2773 established in patients with gallbladder cancer compared with 9 HER2-negative BTC cell lines, of which SNU-2670 is sensitive to tauroumab and SNU-2773 cells are sensitive to afatinib, in addition, afatinib decreased phosphorylation of EGFR and HER2 in SNU-2670 and SNU-2773 cells. Therefore, after the patient signed the consent form, she was treated with afatinib. Because pharmacokinetic studies of trastuzumab showed an average plasma half-life of 5.8 days, and its kinetics were not affected by the combining of these drugs, the patient's condition has been controlled as the result of afatinib combined with BXD, not affected by trastuzumab.

The patient's treatment with trastuzumab was ineffective, but the treatment of afatinib and BXD was effective. There may be two reasons: on the one hand, in the patient's surgical specimen only EGFR and HER-2 genes were detected. Based on the gene profile of GBC, we speculated that afatinib may inhibit the expression of ErbB family in GBC; on the other hand, CM not only alleviates the toxic side effects of Western medicine,

but also has anti-tumor effect.[17] The patient developed diarrhea on the 4th day after taking afatinib. However, after the treatment with BXD in combination with afatinib, the patient's symptoms of diarrhea no longer occurred, and the patient's tumor was controlled during this period. Modern research has found that BXD could prevent and control CPT-11-induced delayed diarrhea, its extract also significantly potentiated apoptotic effects of cisplatin in A549 cells, moreover, apoptosis induced by BXD extract might be the pivotal mechanism mediating its chemopreventative action against cancer.[18,19] An experimental study has shown that the mechanism of BXD treatment of diarrhea may be related to its anti-inflammatory and anti-oxidation, and BXD may involve inhibition of nuclear factor-κB p65 activation and increase of Nrf2 expression in the colorectum.[20] In addition, a study has shown that BXD affected intestinal flora metabolism.[21]

We currently have other patients treated with afatinib and BXD, who are unable to tolerate chemotherapy and gemcitabine-based chemotherapy failure. For the moment, they are stable and we will continue to observe their condition. Thus, we believe that afatinib and BXD treatment can help delay disease progression. We hope that in the exploration of treating advanced GBC, it is possible to find the essence from the chance and find the right people for the treatment of afatinib and BXD to help them improve quality of life and survival. At the same time, we aim to deal with targeted drug resistance.

Electronic Supplementary Material: Supplementary material (Appendixes 1 and 2) is available in the online version of this article at https://doi.org/10.1007/s11655-019-3152-1.

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