Case Report

Celecoxib Combined with Thalidomide in the Treatment of Refractory Neoplastic Fever in Advanced Cholangiocarcinoma: A Case Report

Qiu-yuan Liang1, Kai-Jian Lei1-2*, Shan-Bing Wang3, Yue Ren2 and Yan Xu2

1Department of Oncology, The Second People’s Hospital of Yibin, Yibin, Sichuan, China
2North Sichuan Medical College, Nanchong, Sichuan, China
3Department of Oncology, The Second People’s Hospital of Yibin, Yibin, Sichuan, China

ABSTRACT

Neoplastic fever, a common symptom of tumors, can be mainly controlled by nonsteroidal anti-inflammatories (NSAIDs) and corticosteroids. However, there is no standard treatment guideline for refractory neoplastic fever, which cannot be controlled by the medicines mentioned above. This report presents a case of advanced cholangiocarcinoma with persistent fever lasting 3 weeks. After ineffective treatment with various antibiotics, ibuprofen, and corticosteroids, the body temperature returned to normal after a 48-hour treatment with celecoxib + thalidomide. Finally, the overall survival (OS) of the patient reached 8 months with radiotherapy and chemotherapy.

Background

More than two-thirds of cancer patients have a fever [1]. Neoplastic fever is the second major cause of fever in tumor patients, accounting for 27% [2]. Neoplastic is a paraneoplastic syndrome caused by the tumor, and the mechanism of neoplastic fever is unclear [3]. It may be related to the release of tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6) and interferon (IFN) by tumor cells [4]. Using NSAIDs is the main treatment of neoplastic fever. About 90% patients with neoplastic fever have complete and sustained defervescence within 12-24 hours after taking NSAIDs. Corticosteroids also play an important role in controlling neoplastic fever. About 50% patients with neoplastic fever are defervesced after using Corticosteroids [5]. But no standard treatment guideline exists for refractory neoplastic fever, which cannot be controlled by the medicines mentioned above [6]. Refractory neoplastic fever often leads to delayed systemic chemotherapy [7]. For neoplastic fever patients, defervescence is of great significance to improve their quality of life and get the chance to chemotherapy.

Case Report

On July 16, 2019, the patient who is a 51-year-old woman, came to the hospital and explained that she had had persistent fever and intermittent right upper abdominal distension for more than two months. During this period, she had taken ibuprofen 0.3g q12h for two weeks. Instead of defervescence, her body temperature rose from about 37.5°C to 39°C. After a week of persistent high fever, she came to the hospital. The physical examination showed jaundice in skin and sclera, and Murphy’s syndrome was negative. For the liver function test, total serum bilirubin (TBIL) was 176.2 μmol/L, serum direct bilirubin (DBIL) was 133.8 μmol/L, and indirect bilirubin (IBIL) was 42.40 μmol/L. Serum carbohydrate antigen 199 (CA199) was 134.62U/mL, serum carbohydrate antigen 153 (CA153) was 299.42 U/mL, and serum carbohydrate antigen 125 (CA153) was 180.20 U/mL. An abdominal enhanced CT scan revealed multiple intrahepatic occupancies, and lymph nodes were detected behind the retroperitoneum and hepatic hilar. The largest intrahepatic mass is 9.1cm*7.8cm*9.7cm. She underwent a liver aspiration biopsy, and the pathology showed cholangiocarcinoma (Figure 1). Immunohistochemistry results showed the following indicators: CK7 (+), CK19 (+), CD10 (+), Ki67 (+), about 7%, CD34 (+), Glypican-3 (+), CK20 (-), CDX2 (+), about 7%, 5.6cm*5.1cm*5cm. She underwent a liver aspiration biopsy, and the pathology showed cholangiocarcinoma (Figure 1). Immunohistochemistry results showed the following indicators: CK7 (+), CK19 (+), CD10 (+), P5 (+), HAS (+), Glypican-3 (+), CK20 (-), Ki67 (+, about 7%), CD34 (+). Based on these
examinations, the patient was diagnosed with advanced unresectable cholangiocarcinoma (CCA) T3N1M0 stage IIIB.

**Figure 1:** The pathologic picture.

**Figure 2:** Tumor marker curve.

**Figure 3:** The contrast of abdominal enhanced CT images. A) July 17, 2019: The first CT showed multiple intrahepatic lesions, and lymph nodes were detected behind the retroperitoneum and hepatic hilar region. The largest intrahepatic mass is 9.1cm*7.8cm*9.7cm. B) September 26, 2019: After two cycles of treatment, the lymph nodes are markedly reduced in the hepatic hilar region and retroperitoneum, and the largest intrahepatic mass decreased to approximately 6cm*6.1cm*6.8cm. PR was achieved. C) November 7, 2019: After another three cycles of treatment, the lymph nodes in the hepatic hilar region and retroperitoneum remain stable, and the largest intrahepatic mass decreased to5.6*4.8*6.2cm. D) December 17, 2019: After another cycle of treatment and radiation for metastatic tumors in the hepatic hilar region, lymph nodes in the hepatic hilar region and retroperitoneum got larger and more numerous.

In order to control the patient's persistent hyperthermia, we analysed the blood test, which shows white blood cell (WBC): 19.20*10^9/L, neutrophil (NEU): 17.20*10^9/L, and procalcitonin (PCT): 3.7 ng/ml. The patient had the possibility of biliary tract infection; therefore, piperacillin sulbactam 3g q12 + moxifloxacin 0.4g qd was given for one week. The patient's high fever was still not relieved, and her appetite had decreased. She could only eat 50g rice a day, with severe fatigue. Then, we switched to cefoperazone 2g q8h+ sulbactam sodium 3g qd treatment for one week. The patient’s body temperature remained above 39ºC, and her Karnofsky performance score (KPS) was 30. To lower the patient’s body temperature, dexamethasone 5mg was administered intravenously, so it still doesn’t work. Considering that immunoglobulin M (IgM), immunoglobulin G (IgG) and anti-streptolysin were all in the normal range, blood culture (including aerobic bacteria, anaerobic bacteria, bacteria, fungi, *Plasmodium*) were negative. Therefore, the possibility of refractory neoplastic fever was considered.

All antibiotics were discontinued. Celecoxib 200mg bid + thalidomide 100mg qn were given. After 48 hours of thalidomide + celecoxib, the patient’s body temperature returned to normal. The patient's fatigue was also significantly relieved, and her appetite increased. She ate about 400g rice every day. After 1 week, the patient had a KPS score of 80 and received her first chemotherapy. From July 2019 to February 2020, the patient received 1 cycle of gemcitabine 1g d1 and d8 single-drug chemotherapy and 5 cycles of gemcitabine d1 and d5 + oxaliplatin 200mg chemotherapy. In order to relieve the bile duct compression of the hilar hepatic tumor, on December 24, 2019, portal metastasis VMAT radiotherapy 4000cGy/20F was performed. The OS eventually reached 8 months.

**Discussion**

The incidence of CCA is on the rise worldwide, but the prognosis was poor, with a 5-year overall survival rate of 22-44% [8]. Compared with CCA patients without fever or low fever, patients with high fever (≥38.6°C) have stronger tumor biological invasion, worse immune status, and worse prognosis [9]. The mechanism of cholangiocarcinoma with fever is still unclear, which may be related to the release of TNF, IL-1, IL-6 and IFN by tumor cells [7]. CCA is associated with chronic inflammation, and inflammation has to do with the high expression of cyclooxygenase-2 (COX2) [10]. COX2 increase can stimulate the production of prostaglandin E2(PGE2), resulting in fever [11]. Ibuprofen
is a non-specific COX inhibitor with lower inhibition of COX2 than celecoxib [12]. In this case, ibuprofen failed to reduce the fever while celecoxib + thalidomide succeeded in reducing fever. Celecoxib is 375-fold selective for COX-2, based on human recombinant enzyme assays [13]. Neoplastic fever may be related to the release of TNF, IL-1, IL-6 and IFN by tumor cells and thalidomide has the ability to inhibit TNF and IL-6 [7, 14]. This suggests that specific COX2 inhibitors + thalidomide may be more effective than non-specific COX2 inhibitors in treating refractory neoplastic fever.

A study shows that during the development of CCA, PGE2 produced by high COX2 expression can promote angiogenesis, suppress immunity, and regulate the signaling pathway to stimulate the growth of CCA. This study also demonstrated that COX2 inhibitors inhibit CCA growth by inducing tumor cell apoptosis and controlling tumor cell proliferation [15]. Vascular endothelial growth factor (VEGF) also plays a promoting role in the development of CCA, high expression of VEGF is associated with intrahepatic metastasis and shorter survival. A retrospective study confirmed that the positive rate of VEGF overexpression in cholangiocarcinoma was 53.8% ~ 59.2%, and thalidomide is able to inhibit the expression of VEGF and activate the immune system [16]. Keng-hao Liu established a model of cholangiocarcinoma in rats, and that study provides evidence that thalidomide controls tumor growth by reducing VEGF expression [17]. Relevant researchers point out that thalidomide also controls tumor growth by inhibiting COX2, but thalidomide has a low selectivity for COX2 and cannot completely inhibit the production of PGE2. For patients with high expression of COX2 in tumors, thalidomide can be enhanced with celecoxib [18]. In this case, according to the abdominal CT image, the liver tumor decreased significantly after taking celecoxib + thalidomide combined with chemotherapy. Although the patient eventually died of a blocked bile duct as the tumor progressed, she survived for over eight months. This suggests that celecoxib combined with thalidomide may play a pivotal role in tumor control.

Fatigue is a common symptom in cancer patients, and the hypothesis that activation of the proinflammatory cytokine network explains the main cause of fatigue in patients with cancer: IL1, IL-6, and TNF send signals to the brain, causing fatigue [19]. While there is no standard treatment for fatigue in cancer patients, thalidomide reduces the activity of IL1, IL-6, TNF, and growth factors [20]. In this case, 48 hours after taking celecoxib + thalidomide, the patient's fatigue was significantly relieved. The patient’s KPS increased from 30 to 80. Controlling persistent high fever can improve appetite and reduce fatigue, and it also improves the quality of life of patients. It suggests that thalidomide + celecoxib can be used to improve the low KPS score of patients with severe fatigue and win the opportunity for chemotherapy.

References

1. Browder AA, Huff JW, Petersdorf RG (1961) The significance of fever in neoplastic disease. Ann Intern Med 55: 932-942. [Crossref]
2. Toussaint E, Bahel Ball E, Vekemans M, Georgala A, Al Hakak L et al. (2006) Causes of fever in cancer patients (prospective study over 477 episodes). Support Care Cancer 14: 763-769. [Crossref]
3. Zell JA, Chang JC (2005) Neoplastic fever: a neglected paraneoplastic syndrome. Support Care Cancer 13: 870-877. [Crossref]
4. Johnson M (1996) Neoplastic Fever. Palliat Med 10: 217-224. [Crossref]
5. Chang JC (1988) Antipyretic effect of naproxen and corticosteroids on neoplastic fever. J Pain Symptom Manage 3: 141-144. [Crossref]
6. Tsavaris N, Zinelis A, Karabelis A, Beldieces D, Bacoianis C et al. (1990) A randomized trial of the effect of three non-steroid anti-inflammatory agents in ameliorating cancer-induced fever. J Intern Med 228: 451-455. [Crossref]
7. Rolston KV (2005) Neoplastic fever: all who shiver are not infected. Support Care Cancer 13: 863-864. [Crossref]
8. Farley DR, Weaver AL, Nagorney DM (1995) “Natural history” of unresected cholangiocarcinoma: patient outcome after noncurative intervention. Mayo Clin Proc 70: 425-429. [Crossref]
9. Gong ZI, Cheng JW, Gao PT, Huang A, Sun YF et al. (2019) Clinical Characteristics and Prognostic Factors of Patients with Intrahepatic Cholangiocarcinoma with Fever: A Propensity Score Matching Analysis. Oncologist 24: 997-1007. [Crossref]
10. Rizvi S, Gores GJ (2013) Pathogenesis, Diagnosis, and Management of Cholangiocarcinoma. Gastroenterology 145: 1219-1229. [Crossref]
11. Wójcik M, Ramadori P, Blaschke M, Sultan S, Khan S et al. (2012) Immunodetection of cyclooxygenase-2 (COX-2) is restricted to tissue macrophages in normal rat liver and to recruited mononuclear phagocytes in liver injury and cholangiocarcinoma. Histochem Cell Biol 137: 217-233. [Crossref]
12. Furey SA, Waksmann JA, Dash BH (1992) Nonprescription ibuprofen: side effect profile. Pharmacotherapy 12: 403-407. [Crossref]
13. Lipsky PE, Isakson PC (1997) Outcome of specific COX-2 inhibition in rheumatoid arthritis. J Rheumatol Suppl 49: 9-14. [Crossref]
14. Chaulet C, Croix C, Alagille D, Normand S, Delwail A et al. (2011) Design, synthesis and biological evaluation of new thalidomide analogues as TNF-α and IL-6 production inhibitors. Bioorg Med Chem Lett 21: 1019-1022. [Crossref]
15. Wu GS, Zou SQ, Liu ZR, Tang ZH, Wang JH et al. (2003) Celecoxib inhibits proliferation and induces apoptosis via prostaglandin E2 pathway in human cholangiocarcinoma cell lines. World J Gastroenterol 9: 1302-1306. [Crossref]
16. Yoshikawa D, Ojima H, Iwasaki M, Hiraoka N, Kosuge T et al. (2008) Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. Br J Cancer 98: 418-425. [Crossref]
17. Liu KH, Liao LS, Ro LS, Wu YL, Yeh TS (2008) Thalidomide attenuates tumor growth and preserves fast-twitch skeletal muscle fibers in cholangiocarcinoma rats. Surgery 135: 373-383. [Crossref]
18. Hada M, Horiiuchi T, Shinji H (2006) A case report of unresectable cholangiocarcinoma: patient outcome after noncurative intervention. J Gastroenterol Hepatol 21: 137-142. [Crossref]
19. Wang XS, Woodruff JF (2015) Cancer-related and treatment-related fatigue. Gynecol Oncol 136: 446-452. [Crossref]
20. Sampaio EP, Sarto EN, Galilry R, Cohn ZA, Kaplan G (1991) Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. J Exp Med 173: 699-703. [Crossref]