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Rapidly developing colitis induced by combination therapy of lenvatinib and Anti-PD-1 antibody in the treatment of hepatocellular carcinoma

Jinyuan Ma[2,4#]; Bei Wang[1#]; Quanbao Zhang[3]; Ruidong Li[3]; Conghuan Shen[3]; Jianhua Li[3]; Quangang Zhu[2,4]; Yifeng Tao[3]*; Xiaoyan Qiu[1]*

[1]Department of Pharmacy, Huashan Hospital, Fudan University, 12 Middle Urumqi Road, Shanghai 200040, China.

[2]Shanghai Skin Disease Hospital, School of Medicine, Tongji University, 1278 Baode Road, Shanghai 200443, China.

[3]Department of General Surgery and Liver Transplant Center, Huashan Hospital, Fudan University, 12 Middle Urumqi Road, Shanghai 200040, China.

[4]Shanghai Engineering Research Center for Topical Chinese Medicine, 1278 Baode Road, Shanghai 200443, China.

[#]Co-first Authors.

***Corresponding Authors: Yifeng Tao**

Department of Pharmacy, Huashan Hospital, Fudan University, 12 Middle Urumqi Road, Shanghai 200040, China.

Email: taoyifeng@huashan.org.cn

Xiaoyan Qiu

Department of General Surgery and Liver Transplant Center, Huashan Hospital, Fudan University, 12 Middle Urumqi Road, Shanghai 200040, China.

Email: xyqiu@fudan.edu.cn

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Abstract

Although diarrhea caused by Immune Checkpoint Inhibitors (ICIs) or Tyrosine Kinase Inhibitor (TKI) are common, server colitis caused by tyrosine kinase inhibitor (TKI) combined with anti-PD-1 has not been paid attention to, which is extremely dangerous for patients who were immune compromised or bearing tumor. Lenvatinib is an oral multi-target TKI as the first line treatment for Hepatocellular Carcinoma (HCC). The combination of lenvatinib and anti-PD-1 antibody has been applied for an effort for HCC treatment. Combination therapy of lenvatinib and anti-PD-1 antibody may also amplify the degree of diarrhea or colitis and the related mechanism remains unclear. We reported two cases of initially lenvatinib induced mild diarrhea while fast developed into rather severe colitis after the first dose of anti-PD-1. We speculated that lenvatinib may be a trigger of anti-PD-1 related colitis through mediating the degradation of PD-L1 in colon tissue to make disturbance of immunity homeostasis and increasing the percentage of activated CD8+ T cells infiltration. Prevention and treatment of these related adverse effect were put forward. Further observation of whether the combination of TKI and anti-PD-1 antibody would increase the possibility adverse effect and the mechanism deserved to be done.

Keywords: Lenvatinib; Anti-PD-1; Immune checkpoint inhibitors (ICIs); Immune-related colitis; Multi-target Tyrosine Kinase Inhibitor (TKI); Case report.

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Introduction

Hepatocellular Carcinoma (HCC) is predicted to be the fourth leading cause of cancer-related death globally [1]. From the breakthrough that sorafenib brought to advanced HCC treatment with a median Overall Survival (OS) of 10.7 in 2008 [2], to a non-inferior OS to sorafenib that lenvatinib indicated in 2018 [3], Tyrosine Kinase Inhibitor (TKIs) has been playing an important role in the systematic therapy of HCC. Lenvatinib is an oral multi-target TKI which mainly inhibits Vascular Endothelial Growth Factor (VEGF) receptors 1-3, fibroblast growth factor receptors (FGFR) 1-4. Platelet-derived growth factor receptor-alpha (PDGFRa), RET and KIT proto-oncogenes are also the targets of lenvatinib [4]. As the most recently developed strategies, the combinations of TKIs and immune checkpoint inhibitors (ICIs) have greatly improved the objective response rate (ORR) of HCC. The combination of lenvatinib and anti-PD-1 antibody (pembrolizumab) performed an impressive ORR of 46% with unresectable hepatocellular carcinoma [5].

Tislelizumab is an anti-PD-1 monoclonal antibody. Along with the completion of phase 2 study named Rationale-208 presenting an ORR of 13.3%, tislelizumab was approved for the treatment of HCC patients who were to be enrolled in at least 1 line of prior systemic therapy and the RATIONALE 301 study comparing tislelizumab versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma is now under evaluation [6].

Camrelizumab is an anti-PD-1 monoclonal antibody. The use of camrelizumab was approved in patients with advanced HCC who were previously treated by sorafenib and/or Oxaliber in China. It is evenly matched in mOS of 13.8 months and an ORR of 14.7% [7]. Based on the results of RESCUE, cemrelizumab in combination with apatinib for HCC showed an ORR of 34.3% [8].

Taking the side effects of both TKI and ICIs for consideration, diarrhea and colitis can be found in the reported AEs with various kinds of hypotheses of the related mechanisms. However, few reports were seen to state whether the combination therapy of lenvatinib and ICIs could increase the risk of colitis. Here, we report two cases of immune-related colitis caused by the combination therapy of lenvatinib and tislelizumab or camrelizumab with their severe and fast-developing symptoms soon after the first dose of the anti-PD-1 agent.

Case presentation

A 62-year-old man with hepatocellular tumor underwent a transcatheterarterial embolization. Two days later (August 13th, 2021), he was treated with lenvatinib for 4 mg/d. One week after the first dose, watery diarrhea (8 to 10 times a day) came to the patient without fever, asthenia, nausea, or vomiting. On August 31st, the patient was given a dose of tislelizumab (200 mg). Three days later, the patient reported frequent diarrhea with nearly 40 times a day. He developed melena and the fecal occult blood test showed positive. Subsequently on September 23rd, 2021, the second dose of tislelizumab was administrated and the use of lenvatinib was stopped, but there was no evident relief of diarrhea. Infectious tests including blood and stool cultures were negative. Stool assay reported no Salmonella Typhi, Shigella, Vibrio parahemolyticus. On October 3rd, 2021, Loperamide Hydrochloride Capsules were given upon the symptoms. Then the diarrhea seemed to lessen. On October 6th, the treatment of loperamide was stopped and lenvatinib was started again. However, diarrhea got worsen again so that all the drugs were stopped again 2 days later until the patient was admitted to our hospital. Stool-rt analysis reported positive results of fecal occult blood test (++), Microscopic examination of erythrocyte (17-38HP) and leucocyte (7-9HP) (October 8, 2021). Fluorescent staining of smears showed no mycothallus in excrement (October 20, 2021). Infectious studies including Clostridium difficile detection assay, stool culture, cytomegalovirus (CMV) DNA Polymerase Chain Reaction (PCR) test, and ova and parasites exam were all negative. In all cases, infectious diseases were excluded. At last, colonoscopy indicated erosions on the mucosal surface of the whole colon (October 22, 2021), so PD-1 related colitis was presumptively diagnosed based on the colonoscopy (Figures 1,2). The currently established treatment is intravenous methylprednisolone 20 mg qd and Mesalazine SR Granules 0.5 g tid for his grade 3 colitis. When he was admitted again to out unit for liver transplantation the diarrhea had improved with the decreased frequency of diarrhea 7-8 times a day. After the liver transplantation, this patient initially accepted 80 mg of methylprednisolone intravenously, calcineurin inhibitors and mycophenolate mofetil to suppress the graft rejection. His diarrhea was almost healed, which may also be because of those anti-autoimmune drugs.

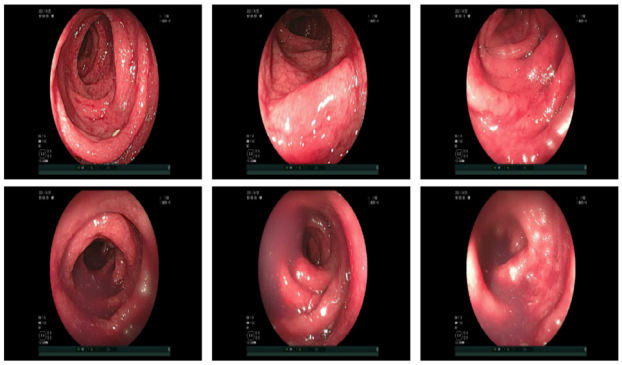

Figure 1: Acute colitis with erosions of the mucosal surface in the whole colon.

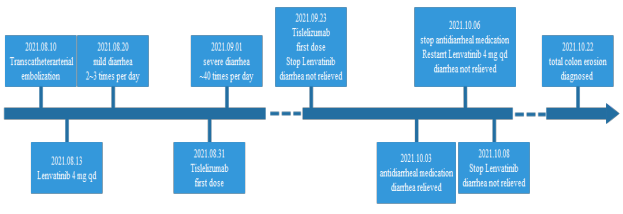

Figure 1: Timeline of the disease and diagnoses.

Another 52-year-old man underwent segmental hepatectomy in 2017 due to HCC while HCC relapsed since 2018 for many times and interventional therapy was done repeatedly. He was treated with lenvatinib since October 2020 regularly. About 7 months later, watery diarrhea (3 to 4 times a day) came to the patient without other infection-related symptoms. In February 2022 he reported fatigue plus poor anorexia and underwent immunotherapy with camrelizumab, an anti-PD-1 antibody, based

on lenvatinib treatment. However, diarrhea got worsen soon after the administration of camrelizumab and he suffered from weight loss. Naranjo scale of this case is 4 and classified as 'possible'.

Discussion

As an multi-target TKI, lenvatinib could mainly target VEGF receptors for not only inhibiting the proliferation of tumor blood vessel but also performing immunomodulatory activity through the vascular endothelial growth factor A (VEGF-A) produced by the tumor cells which can upregulate the expression of immune inhibitory receptors such as PD-1 in CD8+T cells and promote the tumor cell to escape [9]. In addition, FGFR inhibitors were suggested to reduce the population of myeloid-derived suppressor cells, further reduce the proportion of negative-regulatory immune cells, such as MDSC, Treg and TAM, and increase the percentage of activated CD8+ T cells [10]. Recently, Chenhe Yi et al. found that lenvatinib reduced tumor PD-L1 level and Treg differentiation to improve anti-PD-1 efficacy by blocking FGFR4. lenvatinib reinforced the proteasomal degradation of PD-L1 by blocking the FGFR4-glycogen synthase kinase 3β (GSK3β) axis and rescued the sensitivity of interferon-γ-pretreated HCC cells to T-cell killing by targeting FGFR4 [11].

It has been known that the incidence of diarrhea is 39% of reported side effects and adverse reactions [12]. On November 22, 2021, The Pharmacovigilance Risk Assessment Committee (PRAC), the European Medicines Agency's (EMA) committee responsible for assessing and monitoring the safety of human medicines, recommended that colitis as an uncommon undesirable effect should be added to the package leaflet of lenvatinib [13]. However, the mechanism of TKI-related diarrhea is unclear. Since VEGF and VEGF receptors have been shown to be highly expressed in intestines, it is assumed that VEGF inhibition may induce diarrhea by reducing the capillaries network in intestinal villi, leading to ischaemic and hypoxia conditions causing ischaemic colitis [14].

For ICI-related colitis, colonoscopy serves as one of the gold standards for diagnosing ICI-associated enteritis in patients with grade 2 or higher persistent diarrhea. The endoscopic manifestations of ICI-associated colitis are mostly ulcers (57%-79%), erosions, erythema, disappearance of vascular lines, and even normal mucosa [15]. Diarrhea occurred in up to 54% of patients treated with anti–CTLA-4 antibodies. The incidence of GI toxicity of anti–PD-1 monotherapy appears to be much lower, reported to be 19% [16,17]. Diarrhea was not reported to be a common adverse effect when camrelizumab was used alone. While in other combination therapy containing camrelizumab, diarrhea occurred in only 2.0% of the patients.

For the mechanism of ICI-related irAEs, the activation or augmentation of autoimmunity and the disturbance of existing immunity homeostasis can be two ways for us to take consideration. Considering the previous studies, the GI toxicities caused by anti-CTLA-4 antibodies and anti-PD-1 antibodies may present many differences in clinical features and related mechanisms. CD4+ T cells were found in the lamina propria in anti-CTLA-4-induced colitis with a rather high mucosal TNFα concentration observed [17]. CD8+T cells were found in the lamina propria and epithelium in anti-PD-1-induced colitis with predominant Treg cells. Many patients with mild anti-PD-1 antibody-induced colitis may experience stable or slowly escalating symptoms over a relatively long period of time, even with continued immunotherapy in contrast to rapidly progressed colitis driven by anti-CTLA-4 agents. It suggests that other regulatory mechanisms can compensate for the complete loss of mucosal tolerance in colitis driven by anti-PD-1 drugs. It made us wonder that anti-PD-1 antibody-related GI adverse events are more likely to arise due to severe disruption of the immune homeostasis and the trigger factors other than PD-1 blockage may play an important role, such as colonic infections, alterations in the microbiome, dietary changes, and toxic injuries [18].

Actually, PD-1/PD-L1,2 axis is responsible for inhibiting T-cell signaling to provide immune homeostasis [19,20], such as peripheral tolerance in the setting of chronic inflammation [21]. In addition, PD-L1 is upregulated by inflammatory cytokines such as IFN-γ in a wide variety of tissues [22]. Kanai et al. presented a significantly elevated expression of PD-1 and PD-L1 in lamina propria and peripheral mononuclear cells in patients with IBD [23]. Zeinab et al. recently reported that in IBD patients, relative mRNA expression levels of both PD-L1 and PD-L2 were higher than the control groups [24]. Many studies in IBD patients have verified that blocking PD-1/PD-L1,2 can enhance the development of colitis [23,25,26]. The loss of PD-1/PD-L1,2 signaling leads to the expansion of gut antigen-specific CD8+ T cells, which may be the mechanism [27]. Similar results were observed in a multicenter retrospective cohort of patients with underlying IBD (including UC and CD) who were treated with CTLA-4 or PD-(L)1 antibody telling the GI adverse event rate was 41% compared with 11% in a control cohort, implicating the blockage of these immune checkpoints may disturb the remission of IBD [28]. Cassol et al. analyzed the PD-1 and PD-L1 immunohistochemical expression in 15 cases of PD-1 inhibitor-associated colitis and potential mimics – infectious colitis and Inflammatory Bowel Disease (IBD). Increased epithelial expression of PD-L1 was observed in PD1-colitis compared with normal colon and infectious colitis while lower than in IBD. This suggests that PD-L1 epithelial overexpression plays a critical role in protecting the gastrointestinal mucosa from inflammatory-mediated damage. However, PD-1 expression is absent in normal colon and in patients receiving PD-1 inhibitors because PD-1 is neutralized by anti-PD-1 antibodies [30].

For HCC patients weighing less than 60 kg, lenvatinib is usually given at a dose of 8 mg per day as the first-line treatment. In BGB-A317-211, the experimental dose is set at 8 mg or 12 mg based on body weight for lenvatinib plus tislelizumab for a 21-day cycle. For the first patient, lenvatinib was given at a rather low dose of 4 mg per day. Besides, before the first dosage of tislelizumab, the diarrhea was relatively mild compared to the circumstance when the anti-PD-1 agent was given. The contribution of lenvatinib to his colitis was not considered as the main cause. However, compared to CTLA-4 blockage, the colonic inflammation produced by anti-PD-1 or anti-PD-L1 therapy is less frequent, rather mild and usually not rapidly developed [19]. Thus, considering the presence of mild diarrhea before the first dose of tislelizumab and the rapid development of diarrhea when taking lenvatinib, we thought that the 'two-hit' process might happen when anti-PD-1 antibody was given. Besides the reported hypothesis of diarrhea caused by VEGF inhibition, lenvatinib can reinforced the proteasomal degradation of PD-L1 [11]. This mechanism could be the basis of anti-tumor effect but we wondered that if lenvatinib can mediate the degradation of PD-L1 in colon tissue as an off-target effect, thus immune homeostasis was somewhat disturbed, leading to a mild diarrhea as the clinical manifestation. Later, the blockage of PD-1 by anti-PD-1 antibody further caused the fast and severe onset of colitis.

Although those lines of combination therapy of TKI and ICIs are improving overall survival, it should not be overlooked whether the risk of immune-related AE is also increased. We provided detailed case reports of colitis induced by the combination of lenvatinib and PD-1 inhibitor with a rather fast developing pattern. However, more cases are needed to directly monitor if combination therapy can increase the colitis risks and mechanism of irAEs in combination therapy need to be better studied so that precautions could be taken to ensure safe medication.

Declarations

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