Combination of Apatinib and Transcatheter Arterial Chemotherapy Embolization (TACE) for the Treatment of Liver Metastasis of Gastrointestinal Stromal Tumors: Report of One Rare Case

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Abstract

Gastrointestinal Stromal Tumor (GIST) is a type of tumor that originates from mesenchymal tissues of gastrointestinal tract, most commonly in the stomach and small intestine. However, it can occur anywhere in the gastrointestinal tract [1]. More than one-half of the new cases of GIST present with advanced or metastatic disease at diagnosis, and the liver is the most common metastatic organ [2]. For unresectable or recurrent metastatic GIST, imatinib is recommended as a first-line treatment. For imatinib-insensitive and -resistant patients, regorafenib is recommended as a second-line treatment. However, GRID study indicates that the median PFS of regorafenib is only 4.8 months [3].

Apatinib is a small molecule tyrosine kinase inhibitor approved by China Food and Drug Administration in 2014 for the treatment of advanced gastric adenocarcinoma progressed or relapsed after at least two lines of systemic chemotherapy. At present, a large number of studies have shown that it can be applied to a variety of solid tumors such as primary hepatic carcinoma, soft tissue sarcoma, breast cancer, ovarian cancer, etc., with good clinical effects [4-6].

Transcatheter Arterial Chemotherapy Embolization (TACE) is an important therapy for local treatment of liver tumors. According to the NCCN guidelines, TACE was recommended as a treatment method for locally advanced gastrointestinal stromal tumors [3]. So far, there are no studies on the treatment of liver metastasis of gastrointestinal stromal tumors by combination of TACE and apatinib. To the best of our knowledge, this is the first case report of TACE combined with apatinib in the treatment of liver metastasis of gastrointestinal stromal tumors.

Case Presentation

A 51-year-old woman was admitted to our hospital on December 11, 2014, who had suffered from upper abdominal pain with fever and vomiting after eating for 9 days. Blood routine, biochemical examination and Alpha-Fetoprotein (AFP) were normal. Enhanced MRI examination showed that space occupying lesion in the right lobe of liver, considering high possibility of hepatic carcinoma complicating with hemorrhage, with the maximum diameter of 9.86 cm × 9.29 cm; the intrahepatic metastasis was suspected (Figure 1). The patient had a history of intestinal tumor with pathology unknown. She had no indication for surgery after surgical consultation and then transferred to our department. Patient was considered to have hepatic malignant tumor with hemorrhage according...
TACE was performed again, with lipiodol 6 ml + pirarubicin 10 mg with intrahepatic metastasis, indicating disease progression. So the maximum diameter of the tumor was 10.0 cm × 8.6 cm (Figure 7), which was stable compared with the previous image (Figure 6). However, by December 30, 2015, the tumor had slowly progressed to 10.0 cm × 8.6 cm (Figure 7).

On December 30, 2015, CT examination showed that the maximum diameter of the tumor was 8.13 cm × 7.80 cm, which was slightly smaller than before (Figure 4), so the second TACE was performed (Figure 5).

On November 10, 2017, enhanced CT scan of upper abdomen showed that the maximum diameter of the tumor was 14.38 cm × 17.20 cm, which was significantly enhanced (Figure 8), and the angiography showed the blood supply arteries of the tumor were significantly increased (Figure 9). So the patient received TACE treatment again combined with oral administration of apatinib at a dose of 250 mg once a day. On February 23, 2018, enhanced CT scan showed that the maximum diameter of the tumor was 11.20 cm × 9.37 cm, and efficacy evaluation indicated Partial Remission (PR) (Figure 10). Therefore TACE combined with apatinib targeted therapy was performed again. Imaging examinations were conducted on May 22, 2018 and November 2, 2018 respectively, which revealed that the tumor continued to shrink. Besides, no definite tumor staining was seen in angiogram during the course of TACE treatment on November 2, 2018 (Figure 11). On March 29, 2019, the maximum diameter of tumor was 7.81 cm × 8.87 cm (Figure 12), and efficacy evaluation indicated continuous PR.

Sixteen months after oral apatinib treatment, the patient developed proteinuria, with protein 3+ in urine routine test and 3988 mg in 24-h urinary protein quantity. After the suspension of apatinib and the active protection of renal function for a week, the quantitative amount of 24-h urinary protein was reduced to 846 mg, and oral apatinib treatment was started with 250 mg per day again.
Discussion

In this case, the patient was diagnosed with metastatic stromal tumor by liver biopsy and previous history of intestinal surgery, besides PET/CT confirmed no other metastasis. Therefore, local TACE treatment was performed for liver metastatic lesions. In the early stage, the maximum diameter of tumor was reduced from 9.86 cm × 9.29 cm to 8.13 cm × 7.8 cm, so the PFS was 12 months without any adverse events. According to the NCCN guidelines, KIT/PDGFRα mutation detection was recommended to evaluate tyrosine kinase targeted therapy along with local treatment [3], which was refused by the patient for financial reasons, so longer PFS failed to be achieved.

In addition, DSA angiography showed that feeding artery significantly increased after the tumor progressed. It is speculated that the expression of Hypoxia-Inducible Factor-1α (HIF-1α) was up-regulated after TACE, and then that of angiogenesis factor VEGF was increased due to the hypoxic microenvironment of tumor tissues, which led to tumor angiogenesis, resulting in tumor progression [7]. Moreover, TACE treatment, although performed several times afterwards, the tumor got progressed slowly, showing the possibility of TACE resistance. Therefore, it is imperative to take comprehensive treatment of TKI drugs.

GIST was typically driven by tyrosine kinase Kit and the Platelet-Derived Growth Factor Receptor Alpha (PDGFRα), one or more mutations on two specific receptor tyrosine kinases. Among them, 95% of gastrointestinal stromal tumors expressed receptor tyrosine kinase KIT, about 80% of GIST tumors showed KIT mutation, 5% had PDGFRα mutation, and 10% to 15% of KIT and PDGFRα were wild type [8]. Imatinib can inhibit tumor growth by blocking BCR-ABL (a continuously activated tyrosine kinase formed by fusion of chromosomes 9 and 22), KIT and PDGFR. Regorafenib showed significant clinical benefit for GIST patients and significantly improved PFS [9] by inhibiting multiple kinases involved in angiogenesis (including lymphangiogenesis), cell proliferation and tumor growth, and tumor microenvironment [10-12], which was recommended as second-line treatment after failure from first-line TKI treatment.

Studies have shown that apatinib potently suppressed the kinase activities of VEGFR-2, c-kit and c-Src, and inhibited cellular phosphorylation of VEGFR-2, c-kit and PDGFRb, which provides a theoretical basis for our clinical treatment [13]. Therefore, apatinib combined with TACE treatment was given to the patient. After apatinib was administered, the tumor volume continued to shrink from 17.2 cm to 8.87 cm in the maximum diameter, and DSA angiography also confirmed that the tumor staining almost disappeared. As apatinib inhibits VEGFR-2 receptor and tumor angiogenesis, prevents tumor cell proliferation, induces tumor cell apoptosis, and exerts anti-tumor effect. This reconfirms that attention should be paid to the theory of anti-angiogenesis in treatment of GIST. In addition, the patient failed to receive gene test, but patients with GIST are usually complicated with KIT mutation, hence the remission may also be associated with the inhibiting effect of apatinib on Kit expression, but more in-depth studies on molecular mechanism were needed. Up to now, the patient has achieved a PFS of 23 months.

The main side effects of apatinib are hypertension, proteinuria, hemorrhage, hand-foot syndrome, diarrhea, fatigue, etc., which are
mainly Grade 1-2 side effects [14]. Through symptomatic treatment and adjustment of drug dosage, it’s well tolerated by most patients and has little impact on the quality of life. There into, the incidence of proteinuria is about 41%. In our case, the patient developed proteinuria (Grade 3) after oral administration of apatinib, which restored to Grade 1 after suspending oral administration of apatinib and active medical treatment, and then oral apatinib treatment was resumed.

Conclusion

Transcatheter arterial chemoembolization has good local therapeutic effect on liver metastasis of gastrointestinal stromal tumors, which can prolong progression free survival. However, it has certain limitations. Apatinib can be an effective drug in the treatment of gastrointestinal stromal tumors to improve the survival time of patients and improve their survival benefit. At the same time, the combination of the two may achieve better clinical effect, but further clinical trials on large samples are needed.

Authors’ Contributions

XL was a major contributor in drafting the manuscript and revising it critically for important intellectual content and final edition to be published. JZ made substantial contributions to conception and design, acquisition of data, analysis of data, manuscript writing and photo editing. FW gave final approval of the version to be published. FL, JL, NFW participated in making therapeutic regimen and operation of TACE. They all agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References