Clinics in Oncology

Case Report
Published: 15 Apr, 2020

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

Xin Liu, Feng Li, Jun Li, Ningfang Wang, Jian Zhang and Feng Wang**

Department of Interventional Therapy, The First Affiliated Hospital of Dalian University, Dalian, China

Abstract

Gastrointestinal Stromal Tumor is a type of tumor that originates from mesenchymal tissues of gastrointestinal tract, most commonly in the stomach and small intestine. 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. Transcatheter Arterial Chemotherapy Embolization (TACE) is an important therapy for local treatment of liver tumors. According to the NCCN guidelines, TACE was recommending as a treatment method for locally advanced gastrointestinal stromal tumors.

Keywords: Gastrointestinal stromal tumor; Hepatic metastasis; Transcatheter arterial chemotherapy embolizatio; Apatinib; Anti-angiogenesis

OPEN ACCESS

Correspondence:

Jian Zhang, Department of Interventional Therapy, The First Affiliated Hospital of Dalian University, NO 222 Zhongshan road, Dalian 116000, Liaoning province, China, E-mail: 360258430@qq.com

Feng Wang, Department of Interventional Therapy, The First Affiliated Hospital of Dalian University, NO 222 Zhongshan road, Dalian 116000, Liaoning province, China, E-mail: Nil

Received Date: *02 Mar 2020*

Accepted Date: *11 Apr 2020*

Published Date: *15 Apr 2020*

Citation:

Liu X, Li F, Li J, Wang N, Zhang J, Wang F. Combination of Apatinib and Transcatheter Arterial Chemotherapy Embolization (TACE) for the Treatment of Liver Metastasis of Gastrointestinal Stromal Tumors: Report of One Rare Case. Clin Oncol. 2020; 5: 1693.

Background

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 unrespectable 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 recommending 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

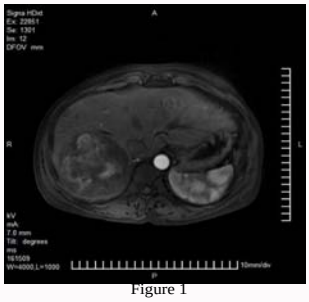

Figure 1

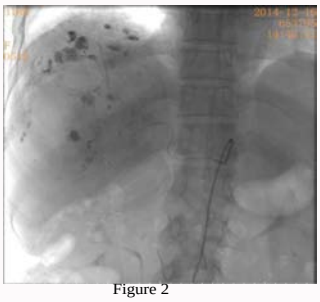

Figure 2

Figure 1,2: The enhanced MRI picture when patient came to our hospital for the first time on December 11, 2014, which showed space occupying lesion in the right lobe of liver (9.86 cm × 9.29 cm), with intrahepatic metastasis. And we performed transcatheter hepatic arterial chemoembolization (Figure 2).

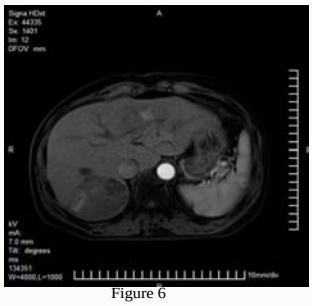

Figure 6

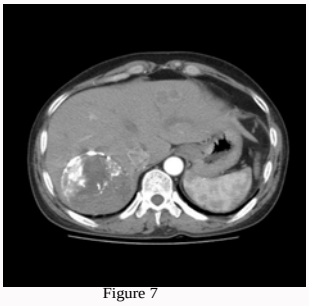

Figure 7

Figure 6,7: The enhanced CT reexamination on August 17, 2015 showed that the maximum diameter of the tumor was 8.13 cm × 7.80 cm, 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).

to imaging examination, and then was treated with transcatheter hepatic arterial chemoembolization, with lipiodol 12 ml + pirarubicin 30 mg + oxaliplatin 200 mg for chemoembolization and PVA 100-300 + self-made gelfoam particles (1 mm^3 × 1 mm^3 × 1 mm^3) for blocking the feeding artery till the end point of embolization (Figure 2), after which the patient recovered well and discharged. On January 28, 2015, enhanced CT reexamination showed that the maximum diameter of the tumor was 8.6 cm × 8.0 cm (Figure 3), with intrahepatic metastasis. Liver biopsy and pathological examination results were consistent with metastatic stromal tumor. Immunohistochemistry: ACTIN(-); CD117(+); CD34(+); CK(-); DOG-1(+); HMB45(-); S-100(-) (Figure 4). In view of this, it was recommended to perform KIT/FDGFRA mutation detection to evaluate whether the patient was suitable for imatinib treatment, which was refused by the family members for financial reasons. On February 2, 2015, TACE was performed again, during which lipiodol 6 ml + pirarubicin 30 mg + oxaliplatin 150 mg was used for chemoembolization and PVA 100-300 for embolization (Figure 5). On March 3, 2015, MR reexamination showed that the maximum diameter of the tumor was 8.11 cm × 7.59 cm, with intrahepatic metastasis. PET/CT examination showed that tumor was seen in left and right hepatic lobes, with FDG metabolism increased, considering metastatic tumor, with no abnormalities found in other organs. Efficacy evaluation indicated Stable Disease (SD). On August 17, 2015, MR reexamination showed that the maximum diameter of the tumor was 8.13 cm × 7.80 cm, with intrahepatic metastasis, which were still stable from last examination (Figure 6).

On December 30, 2015, CT examination showed that the maximum diameter of the tumor was 10.0 cm × 8.6 cm (Figure 7), with intrahepatic metastasis, indicating disease progression. So TACE was performed again, with lipiodol 6 ml + pirarubicin 10 mg + oxaliplatin 150 mg + raltitrexed 4 mg for chemoembolization and PVA 100-300 for blocking blood vessels. Thereafter, on May 9, 2016, December 15, 2016, and July 27, 2017, the patient underwent multiple imaging examinations before TACE, which indicated that the tumor continued to progress slowly. The last examination showed that the maximum diameter of tumor was 12.7 cm × 13.7 cm. The patient recovered after each surgery without adverse events.

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.

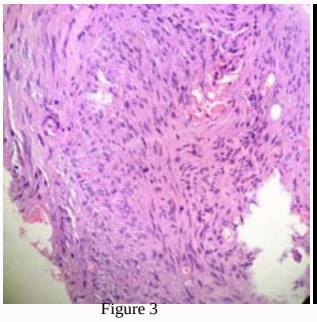

Figure 3

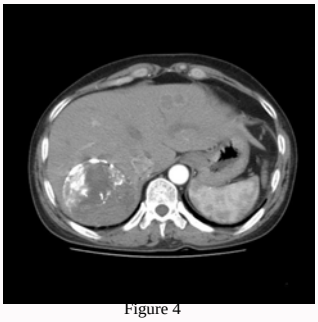

Figure 4

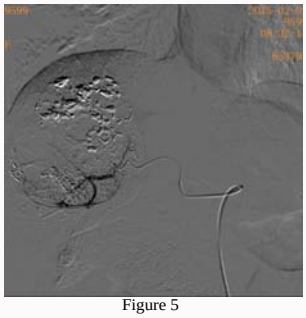

Figure 5

Figure 3-5: The pathology of the lesion in liver showed gastrointestinal stromal tumor. The enhanced CT reexamination on January 28, 2015 showed that the maximum diameter of the tumor was 8.6 cm × 8.0 cm, which was slightly smaller than before (Figure 4), so the second TACE was performed (Figure 5).

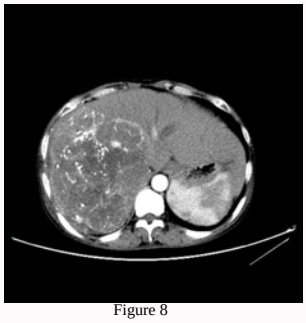
Figure 8

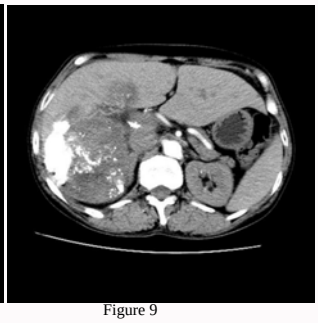
Figure 9

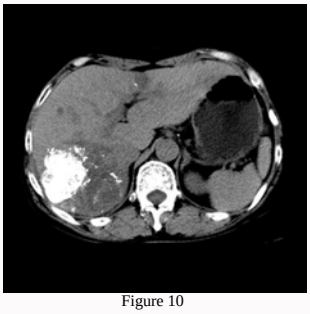
Figure 10

Figure 8-10: On December 30, 2015, the enhanced CT reexamination showed that the maximum diameter of the tumor had progressed to 14.38 cm × 17.20 cm (Figure 8). After 3 months treatment of TACE combined with apatinib, the tumor had remarkably shrunk to 11.20 cm × 9.37 cm (Figure 9), and 16 months after oral apatinib treatment, the tumor continued to shrink to 7.81 cm × 8.87 cm and other intrahepatic metastasis had also remarkably shrunk (Figure 10).

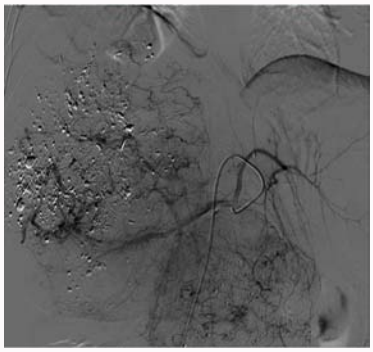

Figure 11: Intraoperative angiography on November 12, 2017 showed the blood supply arteries of the tumor were significantly increased.

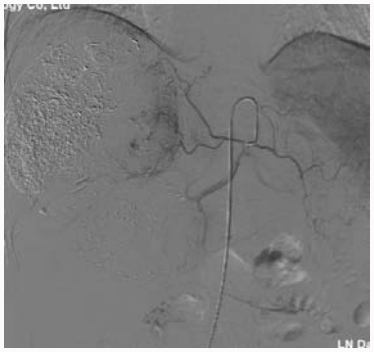

Figure 12: After 1 year treatment of TACE combined with apatinib, no significant tumor staining was seen in intraoperative angiography on November 2, 2018.

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/FDGFRA 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 (PDGFRA), 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 PDGFRA mutation, and 10% to 15% of KIT and PDGFRA 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

1. Chan KH, Chan CW, Chow WH, Kwan WK, Kong CK, Mak KF, et al. Gastrointestinal stromal tumors in a cohort of Chinese patients in Hong Kong. World J Gastroenterol. 2006;12(14):2223-8.
2. Meza JM, Wong SL. Surgical options for advanced/metastatic gastrointestinal stromal tumors. Current problems in cancer. 2011;35(5):283-93.
3. von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Ganjoo KN, et al. Soft Tissue Sarcoma, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(5):536-63.
4. Li F, Liao Z, Zhao J, Zhao G, Li X, Du X, et al. Efficacy and safety of Apatinib in stage IV sarcomas: Experience of a major sarcoma center in China. Oncotarget. 2017;8(38):64471-80.
5. Hu X, Cao J, Hu W, Wu C, Pan Y, Cai L, et al. Multicenter phase II study of apatinib in non-triple-negative metastatic breast cancer. BMC Cancer. 2014;14:820.
6. Lu W, Jin XL, Yang C, Du P, Jiang FQ, Ma JP, et al. Comparison of efficacy between TACE combined with apatinib and TACE alone in the treatment of intermediate and advanced hepatocellular carcinoma: A single-center randomized controlled trial. Cancer Biol Ther. 2017;18(6):433-8.
7. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature. 2000;407(6801):249-57.
8. Heinrich MC, Maki RG, Corless CL, Antonescu CR, Harlow A, Griffith D, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol. 2008;26(33):5352-9.
9. George S, Wang Q, Heinrich MC, Corless CL, Zhu M, Butrynski JE, et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: A multicenter phase II trial. J Clin Oncol. 2012;30(19):2401-7.
10. Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schutz G, et al. Regorafenib (BAY 73-4506): A new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer. 2011;129(1):245-55.
11. Mross K, Frost A, Steinbild S, Hedbom S, Buchert M, Fasol U, et al. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res. 2012;18(9):2658-67.
12. Strumberg D, Scheulen ME, Schultheis B, Richly H, Frost A, Buchert M, et al. Regorafenib (BAY 73-4506) in advanced colorectal cancer: A phase I study. Br J Cancer. 2012;106(11):1722-7.
13. Luo C, Shen J, Ying J, Fang X, Wang X, Fu Z, et al. Case report of a KIT-mutated melanoma patient with an excellent response to apatinib and temozolomide combination therapy. Onco Targets Ther. 2017;10:4553-7.
14. Li J, Qin S, Xu J, Xiong J, Wu C, Bai Y, et al. Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol. 2016;34(13):1448-54.