



Efficacy and safety for the therapy of liver cancer by combination Sorafenib with other therapies: a literature review

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Background and Objective: Liver cancer is one of the top ten cancers in the world with new cases occurring in per year. At present, the etiology and exact molecular mechanism of liver cancer are not fully understood. Today, Sorafenib, as a multi-target drug for the treatment of liver cancer in the world, has made obvious progress in many aspects after decades of clinical trials. Many therapeutic regimens have been created and reached a better prognosis which centered on Sorafenib. In order to get a general understanding of sorafenib in therapy for liver cancer, we review the current status of sorafenib solely or in combination with other therapies for liver cancer treatment.

Methods: The references in this review are from PubMed, web of science and CBM (China biomedical literature service system) with the key words of Sorafenib, HCC and so on. Most of them are published within ten years and their types include clinical trials, meta-analysis, randomized controlled trials and research articles as well.

Key Content and Findings: This article mainly discusses the current situation of clinical application of sorafenib as a targeted drug and the combined therapeutic effect of sorafenib and other therapies, which provides a new way for researchers to improve the clinical efficacy of targeted therapy for liver cancer.

Conclusions: Sorafenib, as the first line drug for patients with liver cancer, has significantly improved the patients' survival by joint or separate way. In the future, more treatment methods may be developed and bring more benefit for liver cancer patients. Of course, some attention should be paid to side effects in patients, including skin redness, hair loss, diarrhea.

Keywords: Sorafenib; liver cancer; treatment

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth major cause of cancer-related death worldwide (1). According to the current research and clinical practice, surgery, chemotherapy and radiotherapy are the most commonly used treatments. However, the side effects of the above therapy methods on the normal human body should not be ignored. For example, Doxorubicin, 5-fluorouracil, Gemcitabine and Irinotecan are all common

chemotherapeutic agents. However, whether used alone or in combination, they both produce large amounts of toxin rapidly in humans. In addition, these medicines did not have obvious outcomes related to the targeted therapy (2). The targeted therapy, as a new therapeutic method, was developed to accurately attack cancer cells. These targeted therapies exert antitumor effects through specific signal pathways, including angiogenesis or cell cycle. As a standard systemic treatment option, it has greatly improved the

survival rate of this devastating disease (3). Sorafenib was the first target therapy approved for advanced renal cell carcinoma (RCC) in 2005. Until now, Sorafenib is still the only one among approved drugs for first-line systemic therapy with a high 10-year survival rate in the treatment of hepatocellular carcinoma (HCC) (4). From 2007 to 2016, many targeted agents were developed. However, most of them in phase II and phase III treatments were not obviously superior compared with sorafenib. Besides, over the past 2 years, 6 new drugs have shown clinical efficacy in phase 3 trials, with substantial progress in testing new and effective systemic therapies. Lenvatinib has successfully become a first-line therapy in clinical practice, and regorafenib, cabozantinib and ramucirumab have been recommended as second-line regimens (5). The trials of Study of Heart and Renal Protection (SHARP) in Asia Pacific region showed that the overall survival of patients with advanced liver cancer treated with sorafenib is 3 months higher than placebo (5). This indicates that sorafenib has obvious advantages over conventional therapy in clinical treatment. But on the basis of this, we naturally want to ask, in combination with other therapies, whether it will prolong the survival time of patients and alleviate the toxic effects of drugs on the body. In order to give readers a general idea of sorafenib for liver cancer therapy, the review will discuss the current clinical application of Sorafenib as a targeted drug, and the combined therapeutic effects of Sorafenib with other therapies, which provides a new administration for researchers to improve the clinical efficacy of targeted therapy for liver cancer. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://biotarget.amegroups.com/article/view/10.21037/biotarget-21-7/rc>).

Methods

The references of this review are obtained from PubMed, Web of science and CBM (China biomedical literature service system). The key words were Sorafenib, HCC, Lenvatinib, radiotherapy, TACE therapy, and so on. The Mesh subjects for search were humans, liver neoplasms, hepatocellular carcinoma, antineoplastic combined chemotherapy protocols and neoplasm recurrence *et al.* Most of literatures were published from 2006.01.01 to 2021.12.31. The clinical trials in the selected literatures must include the control group, the randomized patients group and the treatment by different targeted drugs (6,7). In addition, these trials must have the primary efficacy

endpoint and secondary efficacy endpoints and the statistics variables such as objective response rate (ORR), disease control rate (DCR), and overall survival (OS) (8). The specific strategy was listed in the following table (*Table 1*).

Discussion

The mechanisms and characteristics of sorafenib in treatment for cancer

Sorafenib is not only a new multi-target anti-tumor drug, but also a multikinase inhibitor. It could exert its inhibition on tumor cells and tumor blood vessels at the same time. The experiments *in vitro* revealed that sorafenib could inhibit the proliferation and angiogenesis of tumor cells by acting on target sites of CRAF, BRAF, v600eBRAF, c-kit, Flt-3 in tumor cells and those of CRAF, VEGFR-2, VEGFR-3, PDGFR- β in tumor blood vessels. Among these targets, RAF kinases are serine/threonine kinases, while c-kit, Flt-3, VEGFR-2, VEGFR-3 and PDGFR- β are leucine kinases. These kinases are involved in tumor cell signaling pathway, angiogenesis and apoptosis (9). Common adverse events caused by sorafenib include rash, diarrhea, elevated blood pressure, redness, pain, swelling, and blisters on the palms or soles of the feet. In patients treated with sorafenib, the incidence of adverse events was much higher than that in the placebo group (10). However, these side effects of sorafenib have been reduced by optimizing treatment regimens such as combining with other therapies. In addition, sorafenib also has excellent performance in the treatment of other tumors, such as desmoid tumor (11), renal cancer (12), thyroid cancer and so on (13) (*Table 1*, search MeSH: sorafenib).

Sorafenib and radiotherapy

Radiotherapy, as one of the most commonly used methods to treat tumors, is widely used clinically. It kills cancer cells or shrinks tumors by high doses of radiation. There are usually two radiation ways including external beam radiation and internal radiation. Radiation therapy kills cancer cells or slows their growth by damaging their DNA. However, radiotherapy usually could cause damage to normal cells. Therefore, the combination of radiotherapy and chemotherapy were often used to treat a variety of tumors. A study was performed by Sang min Yoon to treat patients with liver cancer by Sorafenib and external Radiotherapy or Sorafenib alone. The results showed that for patients with advanced liver cancer, Sorafenib and Radiotherapy

Table 1 The search strategy summary

Items	Specification
Date of Search (specified to date, month and year)	2022.01.22
Databases and other sources searched	PubMed, Web of science and CBM (China biomedical literature service system)
Search terms used (including MeSH and free text search terms and filters)	Sorafenib, HCC, Lenvatinib, radiotherapy, TACE therapy, and so on The Mesh subjects for search were humans, liver neoplasms, hepatocellular carcinoma, antineoplastic combined chemotherapy protocols and neoplasm recurrence <i>et al.</i>
Timeframe	2006.01.01–2021.12.31
Inclusion and exclusion criteria (study type, language restrictions etc.)	The clinical trials in the selected literatures must include the control group, the randomized patients group and the treatment by different targeted drugs

treatment improved progression free survival, objective response rate, progression time and overall survival compared with sorafenib treatment (14). The combined treatment of sorafenib and radiotherapy was feasible and induced substantial tumor responses in the target lesions. However, the clinical trial showed that the concurrent use of RT and sorafenib in patients with locally advanced HCC did not confer a significant survival benefit compared with the RT-alone group in either the cohort or PSM cohort. And the side effect of RILD and GI bleeding events after RT showed no significant difference between the groups. Therefore, the regimen of Sorafenib and Radiotherapy needs to be further optimized (15) (*Table 1*, search MeSH: sorafenib and radiotherapy).

Comparative use of Sorafenib and Lenvatinib

Sorafenib is the only systemic VEGF targeted therapy that has been proven to be beneficial to the survival of patients with advanced HCC. The median overall survival (OS) and time to progression (TTP) of Sorafenib were only 1 year and 4 months respectively, with frequent dose reduction or discontinuation due to adverse events (including severe skin toxicity). Therefore, there is still an unmet need for better therapeutic options for patients with advanced HCC (16).

Lenvatinib could bind to the adenosine 5'-triphosphate site of VEGFR2 and its nearby region to inhibit tyrosine kinase activity and related signaling pathways. The preclinical studies indicated that Lenvatinib had a strong antitumor activity by inhibiting the tyrosine kinase activity of VEGFR 1–3 and other carcinogenic and angiogenic pathways driven by FGFR 1–4, RET and PDGFR α . Analysis of angiogenic plasma protein levels in phase I dose escalation test in patients

with advanced solid tumors showed that tumor reduction was associated with increased plasma VEGF and SDF1a levels and decreased plasma soluble VEGFR2 levels (17).

In the phase 3 trial of Lenvatinib versus Sorafenib, the investigators found that Lenvatinib prolonged median survival time by more than one month compared with Sorafenib. Moreover, among various different grades of adverse events, Lenvatinib performed better than Sorafenib (18). In addition, according to the probability sensitivity analysis, in 64.87% of the simulation results, Lenvatinib is a cost-saving measure. However, if the cost of sorafenib is reduced by 57%, Lenvatinib will no longer be able to save costs. But due to the current stable drug prices, Lenvatinib is superior to Sorafenib (19) (*Table 1*, search MeSH: sorafenib and lenvatinib).

Combination of sorafenib and gemcitabine and oxaliplatin (GEMOX)

The GEMOX regimen is being evaluated as a treatment for several cancers, including pancreatic cancer, biliary tract adenocarcinoma, germ cell tumors, and due to the lack of renal and hepatic toxicity, GEMOX combination therapy is in most cases highly attractive for treating HCC patients with underlying cirrhosis (20).

According to the case reported by Boschetti Gilles, a 35-year-old male patient developed cancer in his right liver and received gemcitabine and oxaliplatin (GEMOX) combined chemotherapy. After 12 cycles of treatment, the right parietal lobe and liver metastasis disappeared, and the disease was well treated (21).

Whereas in a phase II randomized trial of Sorafenib alone versus Sorafenib plus GEMOX as first-line

treatment for advanced HCC, there was a trend towards significantly improved PFS and OS in patients treated with the combination of Sorafenib plus GEMOX, which was not observed in patients treated with sorafenib alone. In this combination, chemotherapy was used as a promoter, whereas Sorafenib was used alone in responding patients (22). This illustrates that first-line GEMOX and Sorafenib combined with Sorafenib as maintenance therapy is a clinically encouraging combination therapy for the treatment of advanced HCC. However, because of the toxicity profile, moderate benefit in PFS, and lack of response predictors for the combination of Sorafenib and GEMOX, a follow-up phase III study in unselected patients with HCC is not warranted (22). It can only be said that the combination of Sorafenib and GEMOX provides an option for physicians and patients, and more clinical studies and considerations are needed in the future (*Table 1*, search MeSH: sorafenib and gemcitabine and oxaliplatin).

Advantages of sorafenib combined with TACE treatment

Liver transplantation is the only radical treatment for hepatocellular carcinoma (HCC). However, even in patients with a limited tumor burden that meets the Milan criteria, tumor recurrence after transplantation can hinder the patient's long-term survival. A long waiting time for a liver transplant can also cause the tumor to grow beyond the acceptable standard (23). The use of first-line anti-cancer drugs such as sorafenib can effectively delay the life of patients. In addition, according to Barcelona's clinical liver cancer (BCLC) staging system, transcatheter arterial chemoembolization (TACE) is a first-line treatment for patients with intermediate liver cancer. Since 2004, two TACE techniques have been widely used, namely conventional TACE (CTACE) and TACE with drug eluted beads (DEB-TACE). CTACE was first confirmed to reduce the recurrence of liver cancer after liver transplantation and improve the overall survival rate after transplantation, especially when the waiting time is more than 6–12 months, that is, the treatment for patients with liver cancer applied in the middle stage. It combines transcatheter chemotherapy with lipiodol-based emulsions and embolic agents to achieve strong cytotoxicity and ischemic effects (24). Drug-eluted microbeads TACE (DEB-TACE) is an embolization technique based on the use of microspheres to deliver cytotoxic drugs to the target tumor to achieve the controlled pharmacokinetics of anticancer agents, thereby reducing systemic side effects (25). DEB-TACE has been proved

to be a safe and effective treatment. The microspheres are developed to slowly release chemotherapeutic drugs and increase the intensity and duration of ischemia. The investigators found that in the treatment of patients with unresectable liver cancer, the combination of Sorafenib and DEB-TACE was well tolerated and safe, and most toxicities were related to Sorafenib. The toxicity was manageable by adjusting the dose of Sorafenib, and this therapy is greatly indispensable for patients with unresectable liver cancer in the future (26). The purpose of TACE therapy is to induce tumor necrosis, which is based on the observation that hepatocellular carcinoma is mainly arterial vascularization compared with the surrounding liver parenchyma. This method can promote the combination of cytotoxic effects in tumor tissues with ischemia (24).

Studies have found that the use of TACE alone and the combination of Sorafenib + TACE have different therapeutic effects. In the experiment of Kudo *et al.*, patients with unresectable liver cancer (HCC) were randomly added to the TACE + Sorafenib combination group (80 people) or the TACE group alone (76 people). The results showed that the PFS of the combination treatment group was greater than that of the TACE group alone (27). In addition, in the experiment of Lee *et al.*, it was found that after Sorafenib was discontinued, the survival benefit of TACE and Sorafenib combined treatment seemed to decrease. However, the best time to use Sorafenib is still controversial. In a mouse model that evaluated the effects of Sorafenib withdrawal, it was found that a brief interruption of Sorafenib did not hinder the recovery of tumor response, but the final Sorafenib interruption stimulated the blood vessel to rebound more than never given Sorafenib. In a retrospective cohort study of patients with advanced HCC, it was even confirmed that the continued use of Sorafenib improved the survival rate of patients than that of the discontinuation of Sorafenib (28).

On the other hand, the interim analysis showed promising efficacy results, with almost 50% of patients achieving a partial or complete response after the first TACE cycle and nearly 50% achieving a partial response or stable disease within 2 years after the first TACE cycle. More than 80% of the patients in our study were BCLC B, demonstrating that TACE combined with Sorafenib yields clinically meaningful results in moderate HCC patients (29).

In addition, the use of Sorafenib before interventional therapy can inhibit the vascular endothelial cell growth factor and platelet-derived growth factor receptor induced by hypoxia-inducible factor-1 α , which is considered to

be a factor leading to the further development of tumors. Consequently, TACE combined with Sorafenib can improve clinical outcomes and may become a treatment option for patients with unresectable HCC without vascular invasion or EHS (27) (Table 1, search MeSH: sorafenib and TACE treatment).

Summary

The prospect of sorafenib and its combination with other approaches, as well as future directions in the treatment of liver cancer

Sorafenib, as the first molecularly targeted drug to be marketed in China, has been in clinical application for nearly twelve years. At first, Sorafenib was very exciting in the good treatment effect of HCC, but its challenging side effects should not be ignored. Among them, drug toxicity is the main bottleneck of combination therapy. Palmar-plantar red blood cell paresthesia syndrome (PPES), hypertension, proteinuria, dysphonia, and diarrhea are common side effects caused by drug toxicity. In order to improve the treatment results of Sorafenib, new treatment methods should go beyond the “classical” carcinogenic targets.

As we discussed in the article, Lenvatinib is superior to Sorafenib in some aspects and provides another option for patients. In addition, Sorafenib combined with GEMOX or with TACE, has been a better method for the clinical treatment of liver cancer in recent years, and it broadens the joint therapy for Sorafenib.

To date, the therapy for advanced liver cancer is not satisfactory. In the future, a new medicine or regimen should be created for the therapy of liver cancer patients. For example, Sorafenib could be combined with the CAR-T or tumor immunity method for the treatment of liver cancer, which would possibly bring more benefit for liver cancer patients than the current therapeutic regimen.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://biotarget.amegroups.com/article/view/10.21037/biotarget-21-7/rc>

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form Available at <https://biotarget.amegroups.com/article/view/10.21037/biotarget-21-7/coif>. The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

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