REVIEW

Research Progress in Targeted Therapy of Hepatocellular Carcinoma

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Abstract Hepatocellular carcinoma (HCC) is one of the most common malignancies, and its treatment is limited. With the understanding of key genes and signaling pathways in the occurrence and development of HCC, targeted drugs with high selectivity and low toxicity have been developed continuously, bringing a variety of options for the treatment of advanced HCC. In this article, the research progress on representative drugs of targeted therapy and potential therapeutic targets for HCC are reviewed.

HEPATOCELLULAR carcinoma (HCC) is one of the most common malignancies in the world.^[1] Due to the insidiousness of the onset of HCC and the lack of effective treatment methods, the prognosis of HCC is extremely poor, and the 5-year average survival rate is less than 10%.^[2] It is urgent to develop novel treatment apart from the traditional radiotherapy and chemotherapy for advanced HCC. In recent years, with understanding of the signaling pathways and molecular targets of HCC, breakthrough treatment, represented by sorafenib, has been made in targeted therapy, and has shown advantages in the treatment of advanced HCC.^[3-5] Its high selectivity and low toxicity make it the first-line therapy for systemic treatment of advanced HCC. Other targeted drugs such as lenvatinib and regorafenib have also brought multiple options for the treatment of ad-

vanced HCC.^[6-15] The research progresses of the representative drugs in targeted therapy and the potential targets for HCC are reviewed.

ANTI-ANGIOGENESIS TARGETED DRUGS

Sorafenib

Sorafenib was the first systemic therapy approved for patients with advanced HCC.^[3] The main targets are the vascular endothelial growth factor receptor (VEGFR)1-3, platelet-derived growth factor receptor (PDGFR)- β , etc.^[4] Advanced HCC used to lack effective drug treatment until the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) experiment published in 2007, where sorafenib showed a 44% prolongation of median overall survival (OS) versus placebo (10.7 months vs. 7.9 months; $HR=0.69$) for patients with HCC.^[4] Sorafenib has been used as the first-line treatment of advanced HCC afterwards. However, about 70% of these patients were reported to develop drug resistance 10 years later after clinical introduction of sorafenib.^[5] Li M and his partner successfully formulated a dual-targeting delivery system

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to enhance HCC therapy by encapsulating sorafenib and anti-miRNA21 in arginine-glycine-aspartic acid (RGD) pentapeptide-modified reconstituted high-density lipoprotein (rHDL).^[6] A series *in vitro* and *in vivo* experiments revealed that co-delivery of sorafenib and anti-miRNA21 by RGD-rHDL significantly strengthened the anti-tumor and anti-angiogenic effect of sorafenib with negligible toxicity to major organs, reversed drug-resistance and capability of remodeling tumor environments.^[6]

Lenvatinib

Lenvatinib is a multi-targeted kinase inhibitor, which mainly acts on VEGFR1-3, epidermal growth factor receptor (EGFR)1-4, platelet-derived growth factor receptor (PDGFR)- α . It has been used as the first-line treatment for unresectable HCC without systemic treatment. Studies have found that lenvatinib exerted anti-tumor effects by inhibiting fibroblast growth factor (FGF) signaling pathway^[7] and the FGF receptor-mitogen-activated protein kinase (MAPK) cascade.^[8] A phase III clinical trial conducted by Masatoshi Kudo *et al.* compared lenvatinib with sorafenib in the treatment of unresectable HCC and found that lenvatinib was not inferior to sorafenib in OS, and it significantly improved progression-free survival (PFS), time to progression (TTP), and objective response rate (ORR) of HCC patients; the incidence of adverse events of grade 3 or higher was comparable to that of sorafenib. Therefore, it is reasonable to believe that lenvatinib can be used as a new medicine for advanced HCC.^[9] A cost-benefit analysis showed that lenvatinib was more cost-effective than sorafenib, and has a higher quality-adjusted life year (QALY) due to a longer time period of PFS and lower cost.^[10]

Regorafenib

Regorafenib, a tyrosinase inhibitor, mainly targets PDGFR- α/β and VEGFR-1-3. It is now used as a second-line treatment for HCC. In a randomized, double-blind, placebo-controlled phase III trial (RESORCE) conducted by Jordi Bruix *et al.*,^[11] regorafenib showed higher OS than placebo (median, 10.6 months vs. 7.8 months, $P < 0.05$). This clinical trial suggests regorafenib is effective and tolerable for patients with advanced HCC. Other studies had reached similar results.^[12, 13] A lower Child-Pugh score and a better Eastern Cooperative Oncology Group Performance Status (ECOG-PS) are usually suitable predictors for the second-line

treatment with regorafenib, especially in patients with HCC after failure of sorafenib treatment.^[14] Studies have shown that regorafenib is effective clinically on HCC patients with treatment of sorafenib, regardless of the final dose of sorafenib or tristetraprolin (TTP).^[15] This suggests that regorafenib may be an option of sequential treatment for HCC patients with progressed disease after sorafenib treatment.

Apatinib

Apatinib is a small molecule tyrosine kinase inhibitor. In recent years, it has been found to have a certain effect on HCC. It can selectively bind to and effectively inhibit VEGFR-2, exerting anti-tumor angiogenesis, and can target on endothelial cells and tumor cells both *in vivo* and *in vitro*.^[16] It can also exert anti-tumor effects by inhibiting phosphatidylinositol-3-kinase/Akt (PI3K/Akt) signal transduction pathway.^[17] Retrospective and prospective studies suggest that apatinib is a safe and effective targeted drug for HCC with mild side effects,^[18, 19] although its clinical efficacy is not comparable to sorafenib.^[20] Oral apatinib may cause uniform distribution in human body, so the concentration in liver is limited or insufficient. New formulation, such as apatinib gel which release slowly in body may be a solution.^[21, 22] Transcatheter arterial chemoembolization (TACE) treatment combining with apatinib have shown better therapeutic effectiveness.^[23-25] Moreover, apatinib is cheaper than other targeted drugs for HCC, which makes it an option for patients with limited payment capacity.

Ramucirumab

Ramucirumab is a monoclonal antibody that primarily targets VEGFR-2. A phase II trial by Zhu and colleagues provided preliminary evidence for its therapeutic effect on advanced HCC.^[26] A phase III trial study further confirmed that ramucirumab has significant benefits to survival of patients with advanced HCC.^[27] These results suggest that ramucirumab treatment is associated with better outcome, acceptable tolerability and safety, indicating it could be used as a new drug in the treatment for HCC patients with elevated AFP.^[28]

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody, which binds to VEGF and blocks its biological properties. A phase II trial reported by Abby B *et al.*^[29]

investigated bevacizumab in patients with advanced HCC showed a median PFS of 6.9 months, overall survival rate at 1 year, 2 year and 3 year of 53%, 28%, and 23%, respectively; the grade 3 and 4 adverse events included hypertension (15%), thrombosis (6%, including 4% of arterial thrombosis), and severe hemorrhage (11%). These results suggest that bevacizumab is effective for advanced HCC, but clinicians should be cautious with the risk of severe hemorrhage. Therefore, timely evaluating patient's condition and strictly controlling adaptation sign are important. Bevacizumab combined with sorafenib in the treatment of advanced HCC showed high toxicity and low efficacy in a phase I/II trial, which was eventually terminated.^[30] To the contrast, the combination of bevacizumab with other targeted drugs such as erlotinib has been demonstrated to have a certain effectiveness and tolerability.^[31]

Sunitinib

Sunitinib is an oral multi-targeted tyrosine kinase inhibitor, and its main targets are VEGFR, PDGFR, etc. The results of a randomized phase III trial investigating sunitinib and sorafenib in the treatment of HCC showed that sorafenib with sunitinib was not superior or equivalent but was significantly inferior to sorafenib, with more frequent and severe adverse events.^[32] The results are undoubtedly disappointing. Nevertheless, a phase II trial in 2018 investigating sunitinib combined with transarterial chemoembolization (TACE) for advanced HCC reported a median PFS of 8 months, overall survival of 14.9 months, and the toxic effects and side effects were tolerable,^[33] which provided a new idea in application of sunitinib in the treatment of advanced HCC.

Brivanib

Brivanib is an oral tyrosinase inhibitor which targets dual VEGFR and FGFR. The BRISK-FL study, a multinational, randomized, double-blind, phase III trial investigated the efficacy of brivanib and sorafenib as the first-line treatment of advanced HCC. The result showed that the OS of the brivanib group and sorafenib group was 9.5 months and 9.9 months, respectively; the TTP, their objective response rate (ORR), and DCR were similar. Although the trial did not reach the primary endpoint, these two drugs have been considered to be similar in anti-tumor activity.^[34] In BRISK-PS study which investigated therapeutic effect of brivanib in patients with advanced HCC who were intolerant to

sorafenib or failed to respond to sorafenib, it was concluded that brivanib could not improve the OS.^[35]

Thalidomide and lenalidomide

Thalidomide and its derivative lenalidomide have been recently reported to have antitumor activity. Studies have found that thalidomide can inhibit VEGF and FGF and exert anti-angiogenesis effect.^[36,37] An open-label, single-arm, single-center phase II clinical trial showed that lenalidomide was safe and had modest anti-tumor efficacy as second-line therapy for patients with advanced HCC.^[38]

Endostar

Many studies have suggested that endostar plays a role in anti-angiogenesis.^[39] Endostar can down-regulate the secretion of VEGF, inhibit the ERK, MAPK and FAK cascade signaling pathways, so that exerts anti-angiogenic effect. However, the application of endostar in the treatment of HCC is still in research currently, and its clinical value need further investigations.

Others

There are some other anti-angiogenesis targeting drugs, such as cexiranib, axitinib, linianib, and so forth. Most are still under investigation, and their efficacy and safety seem not satisfied. Cexiranib showed preliminary evidence of antitumor activity for advanced HCC with high incidence of toxicity.^[40] Treatment with axitinib and best supportive care did not improve OS compared to placebo group in the overall study population or in the stratified subgroups.^[41] In a phase III clinical trial, the efficacy of linifanib in the treatment of advanced HCC was not superior to sorafenib, and its safety was not as good as sorafenib either.^[42]

EPIDERMAL GROWTH FACTOR RECEPTOR(EGFR) INHIBITORS

Lapatinib

Lapatinib is an oral small molecule tyrosine kinase inhibitor. The main targets are epidermal Growth Factor Receptor (EGFR) and HER-2 / NEU. It can induce cytotoxicity of cell Huh7, HeG2 and HA22T, and up-regulate autophagy-related proteins to induce autophagy of tumor cells.^[43] It is worth noting that a recent study shows C-terminus of HBx is necessary for the respond sensitivity of HCC to lapatinib,^[44] which suggest that the C-terminus of HBx might be a predictive

biomarker for the treatment response to lapatinib in HCC patients.

Cetuximab

Cetuximab is a recombinant chimeric monoclonal IgG1 antibody. Cetuximab inhibits growth of human liver cancer cells by inhibiting EGFR, which was first reported by Alexander *et al.*, and has served as the theoretical basis for cetuximab in the treatment of HCC.^[45] Studies have shown that the combined blockings of EGFR and PI3K/AKT/mTOR signaling pathways can improve the anti-tumor effect of cetuximab.^[46]

Erlotinib

Erlotinib is a monoclonal antibody that targets EGFR and HER. It has a certain effect on advanced HCC, but the efficacy is limited.^[47] A randomized double-blinded phase III trial showed that sorafenib combined with erlotinib in the treatment of advanced HCC did not improve survivals.^[48] However, a meta-analysis published in 2019 found that combination of bevacizumab with erlotinib was effective and safe for advanced HCC, and can be used in the second-line treatment of HCC.^[49]

THE MAMMALIAN TARGET OF RAPAMYCIN (mTOR) SIGNALING PATHWAY INHIBITORS

Sirolimus

The mammalian target of rapamycin (mTOR) signaling pathway inhibitors have immunosuppressive and anti-tumor effects, and may function as protecting immune grafts and inhibiting tumor growth simultaneously. Yanik EL *et al.* observed the efficacy of sirolimus in the treatment of HCC patients after liver transplantation, and found that sirolimus did not help to reduce all-cause mortality of HCC patients after liver transplantation, but in subgroup of patients older than 55 years it showed better prognosis.^[50] A phase III trial which also examined sirolimus in post-transplantation patients of HCC found that inclusion of sirolimus in immunosuppressive regimens did not improve patients' relapse-free and OS outcomes after 5 years.^[51] The results of these two trials suggest that sirolimus are not beneficial in reducing recurrence and prolonging survival of patients with HCC after liver transplantation.

Temsirolimus and everolimus

Other mTOR inhibitors, such as temsirolimus and ever-

olimus^[52, 53] have not been demonstrated to benefit patients with HCC. Further investigations are needed on proper indication of mTOR inhibitors in patients with advanced HCC.

THE c-MESENCHYMAL-EPITHELIAL TRANSITION FACTOR (c-MET) SIGNALING PATHWAY INHIBITORS

Foretinib

Foretinib is an oral multikinase inhibitor which can inhibit mesenchymal-epithelial transition (MET), reactive oxygen species (ROS), etc. A phase I/II multicentric study on foretinib showed it had good antitumor activity and was well tolerated at a daily dose of 30 mg. The objective response rate was 22.9%, the disease stability rate was 82.9%, and the median OS was 16.7 months.^[54] This study initially confirmed the antitumor activity of foretinib against advanced HCC.

Cabozantinib

Cabozantinib, a tyrosine kinase inhibitor, mainly targets VEGFR, MET, and anaxlektin (AXL). It has been approved for second-line treatment of advanced HCC by Food and Drug Administration (FDA). A randomized, double-blind, phase III clinical trial randomly assigned 707 patients with HCC to receive either cabozantinib (60 mg once daily) or placebo at 2:1 ratio. The results showed that the median OS, and the median PFS of the cabozantinib group was significantly longer than the placebo group (10.2 months vs. 8 months; 5.2 months vs. 1.9 months, respectively).^[55] This study demonstrates that cabozantinib has a certain anti-tumor effect in the treatment of advanced HCC. However, cost-benefit analysis pointed out that for patients with liver cancer who have progressed after sorafenib treatment, cabozantinib is not cost effective for its high cost and drug toxicity.^[56] Therefore, it is imperative to develop relatively economical alternative treatment with good efficiency and low toxicity. Many studies have confirmed the relationship of liver cancer with inflammation and immunosuppressive environment, so introducing immunotherapy into the treatment of HCC may further improve patients' outcome.^[57]

At present, the efficacy of tivantinib in the treatment of primary liver cancer is inconclusive, and further clinical researches are needed. Other c-MET inhibitors, such as golitinib, tepotinib and capmatinib, are currently in stage of clinical trial, and their efficacies

have to be determined.

MITOGEN EXTRACELLULAR SIGNAL-REGULATED KINASE (MEK) INHIBITORS

Selumetinib and refametinib are mitogen extracellular signal-regulated kinase (MEK) inhibitors. The combination with sorafenib alone may have a certain synergy effect and improve its efficacy.^[58] Combination of these two MEK inhibitors with sorafenib in the treatment of advanced HCC showed antitumor activity and acceptable tolerability.^[59, 60] Compared to refametinib alone, combination of refametinib with sorafenib showed synergistic anti-tumor effect in the treatment of advanced HCC, but the adverse events are noteworthy.^[61] Additionally, trametinib and pimasertib are in stage of clinical trial currently; the toxicity and clinical efficacy have to be assessed carefully and are the directions we need to work on.

INSULIN-LIKE GROWTH FACTOR RECEPTOR (IGFR) INHIBITORS

Cixutumumab is a monoclonal antibody against IGF-1R which is closely related to the pathogenesis of HCC. However, in the phase II clinical trial, cixutumumab in the treatment of advanced HCC did not yield meaningful clinical efficacy.^[62] Considering the interaction between the IGF and VEGF signal pathways, a phase I clinical trial study on the treatment for HCC showed that cixutumumab combined with standard dose of sorafenib (4 mg / kg weekly) were effective; the toxicity observed was consistent with that of sorafenib monotherapy.^[63] So, combination therapy may be a potential approach to applying cixutumumab in the treatment of advanced HCC.

NEUROTROPHIN TROPOMYOSIN RECEPTOR KINASE (NTRK) INHIBITORS

Larotrectinib

Larotrectinib, also known as LOXO-101, ARRY-470 and VITRAKVI[®], is a novel oral small molecule, highly selective, broad-spectrum tropomyosin receptor kinase (TRK) inhibitor for children and adults who carry neurotrophin tyrosine kinase receptor (NTRK) gene. Because of the demonstrated good efficacy and safety in a variety of solid tumors with NTRK gene fusion, larotrectinib was approved by the US Food and Drug

Administration (FDA) for the first time on November 2018 to be used in the treatment of adult and pediatric patients with solid tumors that have a NTRK gene fusion without a known acquired resistance mutation.^[64] This means that larotrectinib may play a role in the treatment of HCC patients with NTRK gene fusion.

Entrectinib

Entrectinib is an oral selective tyrosine kinase inhibitor for the treatment of solid tumors with NTRK, ROS1 and ALK fusion.^[65] For metastatic or locally advanced NTRK fusion-positive solid tumors, entrectinib produces durable and clinically meaningful responses in phase I (STARTRK-1) and phase II (STARTRK-2) global study, where entrectinib was taken orally at least 600 mg daily, median follow up was 12.9 months, 7% (4/54) were complete responders, and 50% (27/54) were partial responders. The most common treatment-related adverse events of grade 3 and 4 were weight gain, anemia, and nervous system disorders. No treatment-related deaths occurred.^[66] It can be seen that it is well tolerated, safe and controllable. As larotrectinib and entrectinib has shown certain effect on patients with advanced HCC which is positive for NTRK gene fusion, and these drugs easily pass through the blood-brain barrier, it can be a good choice for patients with advanced HCC and brain metastases.

OTHER POTENTIAL MOLECULAR TARGETS

In addition to the VEGFR and PDGFR molecular targets, there are other molecular targets that have been discovered for the treatment of HCC. For example, animal experiments showed that p38γ promoted the progression of HCC, and p38γ inhibitor inhibited the progress of HCC in a mouse model of cancer. These results suggest that p38γ may become a new target for liver cancer treatment.^[67] Mu-opioid (MOP) receptor was found to be significantly up-regulated in HCC, and its overexpression was related to a poor prognosis of HCC.^[68] In addition, stanniocalcin-1 (STC1),^[69] connective tissue growth factor (CTGF), and cysteine-rich 61 (Cyr61)^[70] have also been reported to be potential therapeutic targets for primary liver cancer.

SUMMARY AND PROSPECTS

Since the advent of sorafenib, researches on targeted therapy of HCC have become the focus.

Afterwards, lenvatinib, regorafenib, cabozantinib and ramucirumab have also shown certain values in the treatment of advanced HCC. In recent years, studies have found that larotrectinib and entrectinib have a certain effective on advanced HCC with NTRK gene fusion.

Apatinib, thalidomide, lenalidomide and endostal alone have poor efficacy in the treatment of advanced HCC, but combined with TACE and chemotherapy can delay the progression of the disease and reduce the recurrence. Similarly, lapatinib alone was not effective in the treatment of advanced HCC, but the C-terminus of HBx may be a predictive biomarker for using lapatinib in the treatment of advanced HCC.

The occurrence and development of tumors are partly caused by the inability of immune surveillance system to detect or destroy cancer cells. Targeted therapy for immune checkpoints in the treatment of advanced HCC deserve more attentions in future.

Conflict of interests

None.

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综述

肝细胞癌靶向治疗研究进展

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摘要

肝细胞癌 (Hepatocellular carcinoma, HCC) 是常见的恶性肿瘤之一, 治疗手段有限。随着肝癌发生发展过程中关键基因和信号通路认识的深入, 一些高选择性、低毒性的靶向药物不断问世, 为晚期肝癌的治疗带来了多种选择。本文综述了肝细胞癌靶向治疗的代表性药物和潜在靶点的研究进展。

关键词: 肝细胞癌; 靶向治疗; 基因; 信号通路; 药物

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