What are the options for hepatocellular carcinoma patients who progress under sorafenib?

Hepatic Oncology

Eunice Y-T Lau¹ & Terence K-W Lee^{*,1}

“...hepatocellular carcinoma treatment has entered a new era with the development of molecular-targeted therapies.”

First draft submitted: 15 February 2016; Accepted for publication: 15 February 2016; Published online: 23 March 2016

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer. It represents the fifth most prevalent cancer worldwide and the third leading cause of cancer mortality, with 55% of all HCC worldwide occurring in Southeast Asia, especially in China and Hong Kong [1]. Curative treatments, such as liver transplantation and hepatic resection, are only applicable to a small portion of patients with HCC as most of the patients are presented at advanced stages when it is inoperable. Historically, systemic chemotherapies including the administration of cytotoxic agents like doxorubicin, cisplatin and 5-fluorouracil were offered to patients with advanced HCC via transarterial chemoembolization (TACE) as the second-line treatment. However, the response rate is disproportionately low as HCC is highly refractory to cytotoxic chemotherapies due to its chemoresistant nature. In the past few years, with improving knowledge of the oncogenic pathways attributing to HCC development, HCC treatment has entered a new era with the

development of molecular-targeted therapies. Currently, sorafenib is the only molecular-targeted agent with US FDA approval for the systemic treatment for patients with advanced HCC. Sorafenib is an oral multi-kinase inhibitor that targets the tyrosine kinases of VEGFR and PDGFR- β , and the serine/threonine kinases of RAF-1 and B-RAF, thereby blocking tumor cell angiogenesis and proliferation. The efficacy of sorafenib in treating HCC was demonstrated in two large-scale, randomized, controlled Phase III trials, the SHARP and the AP trial, in which sorafenib significantly prolonged overall survival (OS) compared with placebo [2,3]. However, the survival benefit achieved by sorafenib was modest, with OS prolonged for only 2.8 and 2.3 months, respectively, when compared with the placebo group, and low response rates of less than 5% as demonstrated in both trials. In real-life practice, nearly a third of patient experienced disease progression with sorafenib and discontinued the treatment [4]. As there are no effective second-line treatment options

KEYWORDS

- biomarker • HCC • PD-1 • resistance
- sorafenib

“In view of the modest effect of sorafenib in treating advanced hepatocellular carcinoma, there is an expanding development of alternative therapeutic agents for the disease.”

¹Department of Applied Biology & Chemical Technology, The Hong Kong Polytechnic University, Hong Kong

*Author for correspondence: Tel.: +852 3400 8799; Fax: +852 2364 9932; terence.kw.lee@polyu.edu.hk

for the sorafenib refractory or intolerant groups at present, the only guideline recommended for them is best palliative care or enrollment to new clinical trials [5]. This urges the need of exploring alternative therapeutic strategies as the first- and second-line procedure for advanced HCC.

The development of new agents for treating advanced HCC

In view of the modest effect of sorafenib in treating advanced HCC, there is an expanding development of alternative therapeutic agents for the disease. Clinical trials on various molecular-targeted agents had been conducted to evaluate their potential in providing survival benefits over sorafenib in treating advanced HCC in first-line setting, including brivanib, erlotinib, linifanib, sunitinib and tigatuzumab [6–10]. However, all of them failed to demonstrate a better survival over sorafenib as first-line treatment. In addition, several clinical trials were also conducted to study the effect of various molecular-targeted agents in patients with sorafenib-refractory HCC, including axitinib, brivanib, everolimus, GC33 and S-1 [11–15]. However, none of them offered survival benefits for the sorafenib-refractory patients. As there are no second-line alternatives for patients with sorafenib-refractory HCC, one of the options for this group of patients is to enroll into different clinical trials. At present, a few other new molecular-targeted agents are being evaluated in different stages of trials for treating advanced HCC.

• New molecular-targeted agents to target angiogenesis & sorafenib resistance

Angiogenesis is an important process for HCC progression. With the successful development of sorafenib as the first-line treatment, a number of molecular drugs targeting angiogenesis are currently under different stages of clinical trials. These drugs include lenalidomide, lenvatinib, regorafenib and cabozantinib and they all demonstrated favorable treatment outcomes in previous clinical trials [16–19]. Apart from targeting angiogenesis pathway, elucidation of the molecular pathways responsible for development of acquired sorafenib resistance is also crucial for HCC cancer therapy. Recent reports showed that acquired sorafenib resistance might be due to activation of alternative oncogenic pathways [20]. Therefore, the use of sorafenib in combination with inhibitors targeting different oncogenic pathways might provide therapeutic benefit. Resminostat is an inhibitor of HDACs. Its mechanism of action is

to inhibit phosphorylation of 4E-BP1 and p70S6k thereby suppressing the AKT pathway, and inhibits histone deacetylation, causing inhibition of the transcription of tumor suppressor genes. Both actions eventually would lead to apoptosis of cancer cells. The combined use of resminostat and sorafenib was evaluated in the Phase I/II SHELTER trial study in which the combination therapy was studied in sorafenib-refractory HCC, with resminostat monotherapy as the control arm [21]. The combination treatment offered a progression-free survival benefit of 2.5 months over the control. Currently, another Phase I/II trial of this combination therapy as the first-line treatment of advanced HCC is being conducted, and its efficacy is compared with sorafenib monotherapy (ClinicalTrials.gov: NCT02400788).

• Molecular-targeted agents for biomarker-selected subgroup of patients

Identification of various biomarkers for the disease allows the stratification of patients who might be responsive to a particular treatment regimen. In the previously randomized, placebo controlled Phase II study, Tivantinib, an oral inhibitor of MET, was found to improve the survival of patients with high MET expression [22]. It is currently under Phase III study to evaluate its efficacy as a second-line treatment for HCC patients with high MET expression who has progressed with sorafenib therapy (ClinicalTrials.gov: NCT01755767). Ramucirumab, a monoclonal antibody against VEGFR2, was found to be associated with better survival only to patients with baseline serum α -fetoprotein level higher than 400 ng/ml [23]. A Phase III clinical trial is underway for treating this subgroup of patients after sorafenib therapy (ClinicalTrials.gov: NCT02435433).

• Monoclonal antibodies for immune checkpoint blockade

Immunotherapy has gained much attention as one of the most recent advances in cancer treatment. One of the most promising approaches to activate the immune system for killing the cancer cells is immune checkpoint blockade. CTLA-4 is the first immune checkpoint molecule to be clinically targeted for treatment of cancer. CTLA-4 is an immune checkpoint receptor expressed exclusively on the surface of T cells, which inhibits T-cell activity and proliferation, resulting in evasion of immune surveillance. Tremelimumab, a monoclonal antibody blocking CTLA-4, has

“Sorafenib is the first and only US FDA-approved molecular-targeted agent that has shown significant improvement of survival of patients with advanced hepatocellular carcinoma.”

been investigated in a Phase II study for HCC treatment [24]. This therapeutic antibody was demonstrated to have a good safety profile and favorable antitumor activity. Currently, this antibody is further evaluated as combination treatment with TACE or radiofrequency ablation (RFA) as they were previously found to induce peripheral immune response (ClinicalTrials.gov: NCT01853618). Another immune checkpoint being targeted for HCC cancer therapy is the PD-1 and PD-L1/PD-L2 pathway. Nivolumab, a fully human IgG4 monoclonal antibody that specifically targets PD-1, was recently approved by the US FDA for the treatment of melanoma and non-small-cell lung carcinoma [25,26]. A Phase I/II clinical trial has been conducted to evaluate its tolerance and anti-tumor activity in sorafenib-refractory HCC patients with or without infection of HBV/HCV viruses [27]. The results showed that this antibody was well tolerated, and produced favorable responses across all drug doses and patient cohorts. Due to this encouraging result, a Phase III trial has just started to compare its efficacy with sorafenib as first-line treatment in patients with advanced HCC (ClinicalTrials.gov: NCT02576509).

Conclusion & future perspective

Sorafenib is the first and only US FDA-approved molecular-targeted agent that has shown significant improvement of survival of patients with advanced HCC. However,

the survival benefits are modest. As there are no other second-line treatments available for advanced HCC after sorafenib treatment, the only options for them are palliative care or enrollment to various new clinical trials. Currently, extensive clinical trials are being conducted for testing the efficacy and safety of various molecular-targeted agents as first- or second-line treatment modalities for advanced HCC patients. Whether these agents would provide better survival benefits to patients as monotherapy over sorafenib, or provide additional survival benefits by given in sequential manner or in combination with sorafenib require further investigation. Better understanding of the molecular mechanisms driving sorafenib resistance, stratification of patients based on biomarkers and interfering with the tumor-immune interactions will open up new therapeutic avenues for advanced HCC patients who progress with sorafenib treatment.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

- Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J. Clin.* 63, 11–30 (2013).
- Llovet JM, Ricci S, Mazzaferro V *et al.* Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.* 359, 378–390 (2008).
- Cheng AL, Kang YK, Chen Z *et al.* Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a Phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 10, 25–34 (2009).
- Bronowicki J, Lencioni R, Venook A *et al.* GIDEON (Global Investigation of therapeutic DEcisions in HCC and Of its treatment with sorafeNib) study first interim results: sorafenib dosing across regions and disease subgroups. *J. Hepatol.* 54, s36–s37 (2011).
- Verslype C, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO-ESDO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 23, vii41–vii48 (2012).
- Cheng AL, Kang YK, Lin DY *et al.* Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized Phase III trial. *J. Clin. Oncol.* 31, 4067–4075 (2013).
- Johnson PJ, Qin S, Park JW *et al.* Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized Phase III BRISK-FL study. *J. Clin. Oncol.* 31, 3517–3524 (2013).
- Cainap C, Qin S, Huang WT *et al.* Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized Phase III trial. *J. Clin. Oncol.* 33, 172–179 (2015).
- Zhu AX, Rosmorduc O, Evans TR *et al.* SEARCH: a Phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *J. Clin. Oncol.* 33, 559–566 (2015).
- Cheng AL, Kang YK, He AR *et al.* Safety and efficacy of tigatuzumab plus sorafenib as first-line therapy in subjects with advanced hepatocellular carcinoma: a Phase 2 randomized study. *J. Hepatol.* 63, 896–904 (2015).
- Kang YK, Yau T, Park JW *et al.* Randomized Phase II study of axitinib versus placebo plus best supportive care in second-line treatment of advanced hepatocellular carcinoma. *Ann. Oncol.* 26, 2457–2463 (2015).
- Llovet JM, Decaens T, Raoul JL *et al.* Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized Phase III BRISK-PS study. *J. Clin. Oncol.* 31, 3509–3516 (2013).

- 13 Zhu AX, Kudo M, Assenat E *et al.* Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. *JAMA* 312, 57–67 (2014).
- 14 Yen CJ, Daniele B, Kudo M *et al.* Randomized Phase II trial of intravenous RO5137382/GC33 at 1600 mg every other week and placebo in previously treated patients with unresectable advanced hepatocellular carcinoma (HCC; NCT01507168). *J. Clin. Oncol.* 32, abstract 4102 (2014).
- 15 Kudo M, Moriguchi M, Numata K *et al.* A randomized, double-blind, placebo-controlled Phase III study of S-1 in patients with sorafenib-refractory advanced hepatocellular carcinoma (S-CUBE). *J. Clin. Oncol.* 33, abstract 4018 (2015).
- 16 Safran H, Charpentier K, Kaubisch A *et al.* Lenalidomide for second-line treatment of advanced hepatocellular cancer (HCC): a Brown University Oncology Group Phase II study. *J. Clin. Oncol.* 30, abstract 4098 (2012).
- 17 Okita K, Kumada K, Ikeda K *et al.* Phase I/II study of E7080 (lenvatinib), a multitargeted tyrosine kinase inhibitor, in patients (pts) with advanced HCC(HCC): initial assessment of response rate. *J. Clin. Oncol.* 30, abstract 320 (2012).
- 18 Bruix J, Tak WY, Gasbarrini A *et al.* Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, Phase II safety study. *Eur. J. Cancer* 49, 3412–3419 (2013).
- 19 Verslype C, Cohn AL, Kelley RK *et al.* Activity of cabozantinib (XL184) in hepatocellular carcinoma: results from a Phase II randomized discontinuation trial (RDT). *J. Clin. Oncol.* 30, abstract 4007 (2012).
- 20 Zhai B, Sun XY. Mechanisms of resistance to sorafenib and the corresponding strategies in hepatocellular carcinoma. *World J. Hepatol.* 5, 345–352 (2013).
- 21 Bitzer M, Giannini EG, Horger M *et al.* Efficacy, tolerability and pharmacokinetics of the oral histone deacetylase inhibitor resminostat in patients with advanced hepatocellular carcinoma: clinical data from the Phase II SHELTER study, abstract 0030. Presented at: *6th Annual Conference of the International Liver Cancer Association (ILCA) Meeting*. Berlin, Germany, 14–16 September 2012.
- 22 Santoro A, Rimassa L, Borbath I *et al.* Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled Phase 2 study. *Lancet Oncol.* 14l, 55–63 (2013).
- 23 Zhu AX, Park JO, Ryoo BY *et al.* Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, Phase 3 trial. *Lancet Oncol.* 16, 859–870 (2015).
- 24 Sangro B, Gomez-Martin C, de la Mata M *et al.* A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. *J. Hepatol.* 59, 81–88 (2013).
- 25 Borghaei H, Paz-Ares L, Horn L *et al.* Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N. Engl. J. Med.* 373, 1627–1639 (2015).
- 26 Wolchok JD, Kluger H, Callahan MK *et al.* Nivolumab plus ipilimumab in advanced melanoma. *N. Engl. J. Med.* 369, 122–133 (2013).
- 27 El-Khoueiry AB, Melero I, Crocenzi TS *et al.* Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040. *J. Clin. Oncol.* 33, abstract LBA101 (2015).