The Management of Advanced Hepatocellular Carcinoma: Are We Making Progress in the Era of Targeted Therapy?

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Introduction

Hepatocellular cancer (HCC) is the sixth- and eleventh-most common cancer worldwide in men and women respectively. It occurs most often in male patients over 40 years of age. It is the most common primary liver malignancy, with an annual incidence of over 500,000 new patients worldwide with more than half of the new cases occurring in China. In the Asia-Pacific region, HCC is the third most common cancer and the second most common cause of cancer-related death. The incidence rate for HCC in the Asia-Pacific region has been rising, linked to a high hepatitis infection rate. On the other hand, the incidence of HCC in Western countries is rising due to the sequels of hepatitis C infection and alcoholic cirrhosis. In the United States, the incidence of HCC almost doubled during the last two decades. There will be a steady rise in the incidence of HCC worldwide due to an increasing prevalence of non-alcoholic steatohepatitis associated with the metabolic syndrome. It becomes one of the important global health problems that physicians have to face, especially in the Asia-Pacific region.

HCC is a cancer of high particular relevance in Hong Kong because of the high prevalence (10%) of hepatitis B infection. It is the second most common cancer causing death in Hong Kong. Current effective treatments for HCC include liver resection, transplantation, various local ablative and trans-arterial therapies. Nevertheless, only around 20% of patients, mostly diagnosed by regular screening, may benefit from these potentially curative surgical therapies. The majority of patients have unresectable HCCs because of advanced tumour stage and poor liver function. Besides, transplantation is indicated only for early small HCCs, and its application is limited by the shortage of liver graft, which is a particularly severe problem in Hong Kong.

Prior to the advent of targeted therapy in HCC, most advanced HCC patients were only palliated by various systemic therapies and in fact a significant proportion of patients were treated by at best supportive care only. Historically, the prognosis of the advanced HCCs was dismal with an overall survival of 2.3-2.6 months. HCC is a relatively chemoresistant tumour and is highly refractory to cytotoxic chemotherapy. There is no convincing evidence so far that systemic chemotherapy improves overall survival in advanced HCC patients. Single-agent doxorubicin has been shown to produce a response rate of about 10-15% but with no proven survival benefits. Nevertheless, significant grade 3 or 4 toxicities, especially neutropenia, are encountered in patients treated with doxorubicin. The newer generation of chemotherapeutic agents, such as gemcitabine, irinotecan and pegylated liposomal doxorubicin, also shows disappointing results. The combination of cisplatin, interferon-alpha-2b, doxorubicin and fluorouracil (PIAF) caused a great deal of enthusiasm at one time. However, in the phase III study, although this combination had achieved seemingly higher response rates than other combinations, there was no demonstrable survival benefits and there were considerable toxicities.

Emerging insights into the biology and molecular signalling pathways in cancer cells has led to the identification of potential targets for intervention and the advent of promising targeted therapy for the treatment of otherwise chemoresistant tumours. In contrast to other solid tumours, HCC has a complex molecular and genetic pathogenesis. Chronic liver injuries, due to either viral infections or environmental toxins play a pivotal role in the carcinogenesis. Many key carcinogenic pathways play a pivotal role in the development of HCCs, and it is difficult to assess which is the driven pathway for hepato-carcinogenesis. Among these targets, exciting clinical results have been shown by targeting the anti-angiogenic pathway and the Raf/mitogen-activated protein kinase kinase-extracellular signal-regulated kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways. Other signalling pathways such as epidermal growth factor receptor (EGFR), and phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) have also emerged as attractive avenues for future therapeutic interventions. Notably, thus far, most of these targets mainly focus on targeting the tumour growth pathway and/or inhibiting tumour angiogenesis.

Sorafenib (Bayer 43-9006; Nexavar) is an oral multi-kinase inhibitor that blocks tumour proliferation by targeting the Raf/MAPK/ERK signalling pathway; it also has significant anti-angiogenic properties attained by targeting the tyrosine kinase VEGFR-2, VEGFR-3 and PDGF receptor β. Recently, two pivotal phase 3 randomised placebo-controlled trials in the West and Asia-Pacific region have clearly shown the survival benefits in using single agent sorafenib in treating patients with advanced HCC: In the SHARP study, 602 patients with biopsy-proven advanced HCC who had not received any prior systemic treatment were evaluated and randomised to receive either sorafenib (400 mg twice daily, n = 299) or a placebo (n = 303). Of note in this study, only patients with Child-Pugh A cirrhosis were included, and 37 (6%) and 56 (9%)
of patients were hepatitis B and hepatitis C carriers, respectively. The results demonstrated a significant improvement in both OS (median 10.7 versus 7.9 months) and TTP (median 5.5 versus 2.8 months) in the sorafenib group versus the placebo group. These results indeed represented a 44% increase in OS (hazards ratio, 0.69; \( p = 0.00058 \)) and 73% prolongation in the TTP (hazards ratio, 0.58; \( p = 0.000007 \)). Sorafenib was generally well-tolerated and serious adverse events only occurred in 13% of patients. Similarly, an Oriental sorafenib study was performed to investigate the efficacy and tolerability of using single agent sorafenib in treating advanced HCC patients in hepatitis-B endemic Asian populations. In this study, a total of 226 patients were recruited and randomised in a 2:1 fashion, i.e. 150 patients on sorafenib and 76 patients on placebo. The disease control rate was 35% in the sorafenib arm. The median OS of patients on sorafenib was 6.2 months which was significantly better than 4.1 months achieved in patients on placebo \( (p=0.0155) \). Based on the results of these two pivotal trials, sorafenib has been approved by the U.S. Food and Drug Administration (FDA) and other regulatory authorities worldwide for the management of advanced HCC patients. Although these two pivotal studies have demonstrated good activity and tolerability in treating advanced HCC patients with sorafenib, most of the enrolled patients belonged to Child-Pugh A cirrhosis with favourable clinical parameters. Therefore, the benefits and safety profile of sorafenib in unselected advanced HCC patients, especially those with Child-Pugh B/C patients or other poor prognostic factors are still unknown. More mature results are needed before recommending the routine use of sorafenib use in Child-Pugh B patients.

The recent development of sorafenib represents a step forward in the treatment of advanced HCCs. However, it is just the beginning of a new horizon in molecular targeted therapy of HCC. It has promulgated strong interests among researchers to unravel more underlying molecular mechanisms of HCC growth and metastasis. Besides sorafenib, other targeting agents have also shown encouraging activity in the treatment of patients with advanced HCC in early clinical trials.

HCC is a highly vascular tumour with a high propensity for vascular invasion, and thus tumour angiogenesis plays a pivotal role in the pathogenesis of HCC. Vascular endothelial growth factor (VEGF) is the most potent known angiogenic factor and its over-expression varies from 37% to 100% in HCC cells, and aberrant VEGF expression is a prominent feature in HCC. The anti-angiogenic effect can be achieved either by using monoclonal antibodies to target the VEGF or employing anti-angiogenesis inhibitor to block various VEGF receptors. Bevacizumab as a single agent, or in combination with other agents has shown modest activity in treating advanced HCCs. In the study conducted by Siegel et al., among 46 enrolled patients with advanced unresectable HCC, single agent bevacizumab achieved a 13% response rate (RR), while 65% of patients had stable disease (SD). Nonetheless, 4% of the enrolled patients had arterial thrombosis and grade 3 or higher haemorrhage occurred in 11% of patients, including one patient who died of varical bleeding. On the other hand, Thomas et al. had performed a non-randomised phase II study of combination of high dose bevacizumab with erlotinib in the treatment of advanced HCC patients. Based on the results of the enrolled patients, the RR was surprisingly high with one patient having complete response, 22% PR and 55% having SD. Moreover, the OS was 15.65 months. Nevertheless, a significant proportion of the enrolled patients discontinued from the study due to treatment-related toxicities and one patient even died from treatment-related adverse events. Sunitinib is another oral anti-angiogenic multi-targeted tyrosine kinase inhibitor with partially overlapping target inhibition with sorafenib. It inhibits VEGF receptor 1-3, PDGFR-\( \alpha \) and \( \beta \), c-kit, Flt-3, colony-stimulating factor receptor type 1 and RET kinases. Although phase II studies employing different doses of sunitinib suggested initial activity of single-agent sunitinib in treating advanced HCCs, a recent randomised phase III sunitinib study was halted early because of concerns about efficacy and treatment-related toxicities. Thus, targeted agents with comparable kinase profiles may produce very different clinical outcomes in similar patient populations. Brivanib (BMS-882664) is another small molecule tyrosine kinase inhibitor of both VEGF and fibroblast growth factor (FGF), receptor family. Raoul et al. reported the results of an open-label phase II study on the use of brivanib both as first-line treatment of advanced HCC patients. In this study, when brivanib was used as first-line treatment of 55 advanced HCC patients, the overall RR was 5%, while another 47% of the patients achieved SD. The TTP was 2.8 months. Currently, brivanib as a single agent is being investigated in large-scale phase III randomised studies either as first-line therapy compared with sorafenib or as second-line treatment after sorafenib failure for advanced HCC patients. Last but not least, linifanib (ABB-869) is another novel orally active, potent and selective inhibitor of the VEGF and PDGF families of receptor tyrosine kinases. Toh et al. recently reported the results of a phase 2 trial of ABB-869 in advanced HCC. In this open-label, multicentre phase II trial, oral ABB-869 was administrated in patients with both Child Pugh A and B cirrhosis. The median OS of the enrolled patients was approaching one year. Based on this preliminary results, a randomised phase III trial is underway to assess the efficacy and tolerability of ABB-869 compared with sorafenib as first line treatment for patients with advanced HCC.

While sorafenib and other anti-angiogenic multi-targeted tyrosine kinase inhibitors show early promises in the management of advanced HCC patients, most of these targeted agents have demonstrated very low response rate when they are used alone. They will not induce radiological regression of the tumour but rather result in mostly disease stabilisation. Thus, the other direction in the future systemic trials of treatment of advanced HCC is to test the potential benefit of combining sorafenib together with various systemic agents to increase the response rate and downstage the tumour for potential curative resection. By adding other systemic agents to sorafenib, there is a potential for gaining additional efficacy through possible synergistic effects. To this end, several investigators are trying to investigate the benefits of adding either novel molecular targeting agents, biological agents or chemotherapeutic agents to enhance sorafenib efficacy. In particular, there are preliminary data in the literature suggesting...
potential benefits in combining sorafenib with various chemotherapy agents to enhance sorafenib activity. The results from a randomised phase II study by Abou-Alfa et al. showed encouraging activities in combining sorafenib with doxorubicin in the treatment of advanced HCC patients. This study has suggested possible synergistic actions between sorafenib and doxorubicin as sorafenib may potentially inhibit the Ras/Raf/MEK/ERK pathway, which in turn may prevent activation of the multidrug resistance pathway. Notably, more than one-third of the recruited patients experienced significant treatment related toxicities, such as febrile neutropenia and treatment-related death. Instead of using doxorubicin as the chemotherapy partner, our group at Queen Hospital, the University of Hong Kong has reported the results of a multi-centre phase II study of combining sorafenib with capcitabine and oxaliplatin (SECOX) in the treatment of advanced HCC patients. Our results demonstrated promising activities with an overall RR of 16% and OS 11.8 months. Moreover, this regimen was well-tolerated by most enrolled patients. In view of this promising result, a large scale randomised phase III Asia-Pacific study is underway to investigate the benefits of this regime over single agent sorafenib in the treatment of advanced HCC patients. Clinical trials of combination of sorafenib with various other chemotherapeutic agents, such as fluoropyrimidine, platinum compounds and gemcitabine are still in the stage of active patient recruitment and the results will be eagerly awaited.

Conclusion

In summary, in the era of targeted therapy, there are some real progresses made in the systemic treatment for advanced HCC patients. The recent development of single agent sorafenib in the treatment of advanced HCC patients indeed represents a major milestone in the treatment of advanced HCC. It proves the concept that molecular targeted therapies, especially anti-angiogenic agents, play a pivotal role in the treatment of HCC. Nevertheless, our current understanding of the underlying pathogenesis of HCC is still very primitive. More in-depth basic and translational researches need to be done to further elucidate the underlying molecular pathogenesis in the disease. The future direction in improving the survival of advanced HCC patients will likely rely on either combining sorafenib with others to circumvent the complex signalling pathways in HCC or the development of novel targeted agents which can target the main oncogenic driving pathway in the disease.

References

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