Features and treatment options of Chinese hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. More than 53% of the total HCC patients in the world come from China. The absolute number of new Chinese HCC cases still keeps increasing and it remains a most dominant cancer burden in the next several decades. Compared to the HCC occurred in Europe and North America, Chinese HCC patients have their own special features in etiology, demographic features (risk factors, age of onset, gender distribution time trend of incidence), biological behavior, clinical manifestation, treatment strategy and prognosis. The success or failure of a series of clinical trials related with systemic therapy for advanced HCC can be partly attributed to those features of Chinese HCC. Thus it is suggested that new trials should be performed respectively for Chinese HCC patients from the Western population, like the success of sorafenib SHARP and ORIENTAL studies. The protocal design, organization and practice of trials in HCC of China should be made individually to avoid or reduce the possible heterogeneity of HCC populations and facilitate the personalized therapy of HCC. The present review discussed the features and treatment options of HCC in China that maybe help to understand the clinical course for Chinese patients with HCC. More importantly, the future strategies for clinical trials of Chinese HCC were emphasized.

Keywords: Hepatocellular carcinoma (HCC); incidence; etiology; personalized therapy; China

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Features of Chinese hepatocellular carcinoma (HCC)

Primary liver cancer (PLC), mainly consisted of HCC, is the fifth most common cancer and the third most common cause of death from cancer worldwide. It has been estimated that there are above 749,000 new cases of liver cancer (523,000 in men and 226,000 in women) and 695,000 deaths (478,000 in men and 217,000 in women) per year around the world in 2008. In China, HCC is also one of the most popular cancers. More than 401,000 new patients (53.5% of the world) are diagnosed with liver cancer and more than 371,000 patients (53.4% of the world) are killed by the terrible disease annually (1).

Based on the national cancer sample survey data during 1998-2007, the PLC incidence was 25.84/100,000 in China, with an age-standardized rate (ASR) of 18.82/100,000. The annual percent change (APC) of urban male and female liver cancer incidence rates were 1.1% and –0.5%, with ASR at –0.5% and –1.9% individually; While the APC of rural male and female liver cancer incidence rates were 3.7% and 3.1%, with ASR at 1.9% and 1.3% respectively (2). The Chinese PLC incidence is expected to increase in the following decades but its ASR will decrease slightly. The PLC absolute number will keep increasing and remain a most dominant cancer burden in China in the next several decades.

From the data released above, the fatality ratio of

mortality to incidence can be calculated to be 0.93 for both the total world and Chinese population. It is very close to 1.00, indicating that most patients who were diagnosed with PLC will die within one year. The poor outcome of HCC is mainly due to it rarely presents with specific or obvious symptoms at early stage. Actually, nearly 80% of patients have progressed to the advanced stage and lose the chance of curative hepatectomy when the diagnosis of HCC was made (3). The median survival for HCC after diagnosis with supportive care ranges from approximately 6 to 9 months in Western countries and only 3 to 4 months in East Asian countries (4). HCC is always deemed as one of the most aggressive tumors in East Asian countries as well as China.

The possible etiology for HCC is manifold, including hepatitis virus infection, exposure to aflatoxins, water pollution (blue-green algae toxins), excessive alcohol consumption, tobacco smoking, and non-alcoholic fatty liver diseases (NAFLD) plus obesity, plus other less common etiologies (5). However, there is a wide variation in the predominant risk factors for different populations. Chronic infection with hepatitis B virus (HBV) remains the overwhelming cause of HCC in China, where the prevalence of hepatitis B is nearly 10% in the general population (6,7). Whereas in Western countries, such as the United States, Europe and Japan, where hepatitis B is rare but hepatitis C is the major cause of HCC. In addition, the alcohol-related cirrhosis usually due to alcohol abuse also play a non-neglectable role in the carcinogenesis of HCC in Western developed countries (8). That is the most important difference in the etiology of HCC between Chinese patients and those in developed countries.

Besides the etiology and risk factors for Chinese HCC patients is unique, some other demographic features, e.g., age of onset, gender distribution and change of incidence rate over time for HCC between China and Western developed countries are also greatly distinct.

From the statistics between year 2000 and 2005 presented by Professor Jin-Lin Hou, Nanfang Hospital, Guangzhou, China, the incidence of HCC in Chinese population increases with age. For every age stratum, males have a higher incidence of HCC compared to females. The ASR are 58/100,000 persons for men and 22/100,000 persons for women, and male-to-female ratio is nearly 3:1 (9).

The common age of HCC at onset is 40-60 years. Although the incidence of HCC is relatively low for women below the age of 40 years (<3/100,000), it is already at 21/100,000 for men between the ages of 35 and 40 years. This incidence increases proportionally with age in both sexes from the age of 40 onward, reaching >160/100,000 for males and 94/100,000 for females after the age of 70 years (9).

With national vaccination program against hepatitis B since 1990s, the incidence of HBV-associated HCC is estimated to be decreased in China after several decades later. However, the HCC might still be a severe disease burden for Chinese people because the seemingly rising prevalence of hepatitis C infection and alcohol abuse in recent years in China (10). HCC is still the dominant cancer to be prevented and controlled in China in the following several decades.

Current treatment options of Chinese HCC

Current treatment options for HCC in China are multi-disciplinary, and the use of available treatment depends on liver function and tumor stage. Generally speaking, the treatment strategies could be divided into two main fields: surgical and non-surgical approaches. Surgical techniques for HCC usually include radical lesion resection, liver transplantation, and palliative surgery; Non-surgical techniques include trans-catheter arterial chemoembolization (TACE), radiotherapy, immunotherapy, systemic chemotherapy, molecularly targeted therapy, and traditional Chinese herbal medicine (e.g., Pishuang, mainly consisted of arsenic acid). In addition, several types of local-regional ablation therapy, including anhydrous alcohol injection and radiofrequency, are also used in clinical setting of China.

HCC can be treated curatively with surgical resection, liver transplantation, or radiofrequency ablation, but only 15% of patients are diagnosed at a stage where curative treatment is possible. In China, the early stage of HCC is referred to as “small HCC” (carcinoma with a maximum diameter ≤3 cm). For those patients with early disease who present with solitary tumors and good liver function, 5-year survival rates of greater than 50% are observed after surgical resection. However, as most HCC patients in China have progressed to the advanced stages at the time of diagnosis, they are unfortunately ineligible for surgical resection and other potentially curative treatments.

When patients are diagnosed at an advanced stage of HCC, as are 80% of all cases, median survival times are less than a half-year. In such a case, embolisation or chemoembolisation, often are regarded as the important options in China and survival advantages have been identified in well-selected candidates. However, for the

patients not suitable for chemoembolisation, a significant effective medical strategy is greatly needed to treat advanced HCC in China.

In the past several decades, systemic chemotherapy is also commonly used in China, despite the lack of evidence of a survival benefit (11). For example, the PIAF regimen (cisplatin, IFNa, doxorubicin, and infusional 5-FU) was one of the best-studied regimen for Chinese patients with advanced HCC (12-14). Particularly, in a randomized phase III study, PIAF (cisplatin 20 mg/m^2 on days 1 through 4, IFNa 5 MU/m^2 subcutaneously on days 1 through 4, doxorubicin 40 mg/m^2 on day 1, and 5-FU 400 mg/m^2 on days 1 through 4) was compared to single doxorubicin (60 mg/m^2 every three weeks) in 188 unselected patients with chemotherapy-naive unresectable HCC. While objective response rates were higher with PIAF (21% *vs.* 11%), this difference was not statistically significant, nor was the difference in median survival duration (8.7 versus 6.8 months, P=0.83). Treatment-related toxicity was more pronounced with PIAF (neutropenia 82% *vs.* 63% grade 3 or 4, thrombocytopenia 57% *vs.* 24% grade 3 or 4, hypokalemia 7% *vs.* 0% grade 3 or 4) (15).

The failure to show a survival benefit in this trial may be attributed to the lack of patient selection. The importance of liver function to the response with the PIAF regimen was demonstrated in a series of 149 patients with unresectable HCC who were treated with PIAF (13). The objective response rate was significantly higher in patients with a normal bilirubin and a non-cirrhotic liver compared to those with cirrhosis and a serum bilirubin >0.6 mg/dL (50% versus 6%).

Recently, FOLFOX, serial regimens containing oxaliplatin plus short-term infusional 5-FU and leucovorin which are most commonly used in the treatment of advanced colorectal cancer, has been reported to be active in Chinese HCC. In a recent published phase III trial (EACH study), 371 patients with advanced or metastatic HCC were randomly assigned to FOLFOX4 versus single doxorubicin (50 mg/m^2 intravenously every 3 weeks) across 38 centers in four Asian countries (16). Approximately 90% of patients in both arms were positive for HBV infection and approximately 80% in both arms had Barcelona Clinic Liver Cancer (BCLC) stage C disease. At the pre-specified final analysis, median OS was 6.40 months with FOLFOX4 and 4.97 months with doxorubicin (P=0.07). Median PFS was 2.93 months with FOLFOX4, and 1.77 months with doxorubicin (P<0.001). ORR was 8.15% with FOLFOX4 and 2.67% with doxorubicin (P=0.02). On continued follow-up, the trend toward increased mOS with FOLFOX4 was maintained (6.47 months with FOLFOX4 *vs.* 4.90 months with doxorubicin, P=0.04). Toxicity was consistent with previous experiences with FOLFOX4; Proportions of grade 3-4 adverse events were similar between treatments.

Clearly, FOLFOX4 showed a lower OS and PFS benefit in Asian HCC (6.40 and 2.93 months) than that brought by GEMOX (11 and 4.5 months) or XELOX regimen (9.3 and 4.1 months) in European HCC patients (17-20). Systemic chemotherapy may be less effective overall in HCC patients with severe liver cirrhosis. This was illustrated in an evaluation of predictive factors among 147 patients receiving chemotherapy for HCC. There were no objective responses among patients with a poor performance status, ascites, portal vein tumor thrombus, or serum total bilirubin >2.0 mg/dL (21). The great difference as to the underlying cause of cirrhosis for Asian HCC, HBV rather than alcohol or HCV, and therefore a possible worsen hepatic reserve may accounted for the survival difference.

Approval of sorafenib as the first molecularly targeted therapy for treatment of advanced HCC represents a milestone in the treatment of the disease. The results from the phase III trial (SHARP study) have shown a survival benefit compared to best supportive care alone (22). The multicenter SHARP trial in European and America randomly assigned 602 patients with inoperable HCC and Child-Pugh A cirrhosis to sorafenib (400 mg twice daily) or placebo. The primary endpoint OS was significantly longer in the sorafenib-treated patients (10.7 *vs.* 7.9 months), as was time to radiologic progression (5.5 *vs.* 2.8 months). Treatment was well tolerated with manageable side effects. These results established sorafenib monotherapy as the new reference standard systemic treatment for advanced HCC.

The efficacy and safety of sorafenib in Asian patients was demonstrated by a second placebo-controlled phase III trial (Oriental study) in the same time. A total of 226 patients with Child-Pugh A cirrhosis and no prior systemic therapy for HCC received sorafenib 400 mg twice daily or placebo. Patients receiving sorafenib had significantly better mOS (6.5 *vs.* 4.2 months) and mTTP (2.8 *vs.* 1.4 months) (23).

The survival benefit was markedly less in this trial than that achieved in the SHARP study. Factually, the treated group in the Asian trial had shorter survival duration than the control group in the SHARP trial (6.5 *vs.* 7.9 months), despite the both trials used the same entry criteria. The possible reason might lie in the fact that patients enrolled in the Asian trial were more ill at the start of therapy

than those in the SHARP study, with a generally worse performance status and more advanced stage of disease (24).

The difference in response to sorafenib between different populations might be explained partly in terms of the etiology of the HCC. Asian patients have a higher prevalence of infection with HBV as compared to Western populations; 73% of the patients enrolled to the Asian trial had HBV infection versus 18% of those enrolled to SHARP (21,22). At least some exploratory analyses suggest that patients with HCV infection as the etiology of their cirrhosis may have a better response to sorafenib as compared to those with other underlying causes of cirrhosis (25). As an example, in an exploratory analysis of the phase III SHARP trial, although a survival benefit was seen in all subgroups treated with sorafenib, the difference in median overall survival between sorafenib and placebo-treated patients was highest in those with HCV-related cirrhosis (6.6 months, 14 versus 7.4 months); It was 3.6 months (9.7 versus 6.1 months) in patients with HBV-related cirrhosis, and 2.3 months (10.3 versus 8 months) in those with underlying alcohol-related liver disease (25). These differences in outcome according to hepatitis virus type could potentially explain some of the survival differences between the SHARP and Asian trials of sorafenib.

Future strategies for clinical trials of Chinese HCC

There have been many clinical trials since the success of sorafenib to look for further targeted therapies to offer patients with advanced HCC. Randomized phase III trials of other novel targeted agents including sunitinib, linifanib, brivanib, and the combination of sorafenib plus erlotinib have failed to improve overall survival compared with sorafenib as a single agent in the first line setting, as well as compared with placebo in the second-line setting, in the case of brivanib. These negative studies are a sobering reminder of the challenges to clinical study in HCC, including the competing comorbidity of liver dysfunction, marked clinical and biologic heterogeneity, and the unreliability of surrogate endpoints to accurately predict survival (26).

More detailed speaking, the main reasons for the failure of these systemic therapies might be lied in the following four important factors. (I) Firstly, ignoring the great heterogenicity in etiology and clinical features of HCC between Asian and Western patients and pooling them into the same one study; (II) Secondly, underrating of particularity of HCC, which frequently occurs in the setting of chronic hepatotisis and cirrhosis. The diagnosis of HCC factually implies three types of diseases including chronic hepatotisis, cirrhosis, and liver cancer simultaneously. This factor must be made into consideration when clinical practice executed and the anticancer therapy must be accompanied with antiviral and hepatoprective agents. The lack of the latter two in the treatment of HCC would inevitably discount the anticancer effect of new drugs; (III) Thirdly, there still is no well-recognized molecular typing (gene type) available for HCC and the biomarker-driven personalized therapy of HCC is faraway until now. In the future, the participants enrolled into trials should be chosen under the guide of genotype. The candidate novel agent or regimen for systemic therapy of HCC should be designed to fit a specific population, not fit all population with great heterogenecity; (IV) Lastly, the stratifying strategy on subgroup analysis was not desired. When subgroup analysis conducted, the difference in region, hepatic function, TNM stage, and vascular invasion should be considered independently as the possible stratifying factors. Virtually, the aim of the stratification is to reduce the impact of population heterogenecity as great as possible and screen the predominant population for a specific therapy.

Conclusions

HCC is a more aggressive tumor that frequently occurs in the setting of chronic liver disease and cirrhosis. Hepatic reserve often decides the therapeutic options. Systemic therapy for HCC is an evolving field in recent years. The response to systemic treatment depends on ethnicity and cause of cirrhosis to some extent. Systemic therapy for HCC needs to be intensively investigated in the future.

In the design of following new trials for HCC, a key point must be specially considered is that Chinese HCC largely differed from HCC patients in Western developed countries in etiology, biological characteristics, treatment strategies and prognosis. Based on these unique features of Chinese HCC, new trials should be performed independently from the Western population, like the success of SHARP and ORIENTAL studies. The protocol design, organization, conduct and practice of trials for Chinese HCC patients should be made individually to avoid or reduce the possible heterogeneity of HCC populations and facilitate the personalized therapy of HCC. It comes personalized or individualized medicine time now. Thus even clinical trial should be personalized or individualized,

namely one should fit one, not one fits all.

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