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The evolving landscape of therapeutic drug development for hepatocellular carcinoma

Dawn Qingqing Chong *, Iain Beehuat Tan, Su-Pin Choo, Han Chong Toh

Department of Medical Oncology, National Cancer Centre Singapore, Singapore

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ABSTRACT

Currently, only one drug, sorafenib, is FDA approved for the treatment of advanced hepatocellular carcinoma (HCC), achieving modest objective response rates while still conferring an overall survival benefit. Unlike other solid tumors, no oncogenic addiction loops have been validated as clinically actionable targets in HCC. Outcomes of HCC could potentially be improved if critical molecular subclasses with distinct therapeutic vulnerabilities can be identified, biomarkers that predict recurrence or progression early can be determined and key epigenetic, genetic or microenvironment drivers that determine best response to a specific targeting treatment can be uncovered.

Our group and others have examined the molecular heterogeneity of hepatocellular carcinoma. We have developed a panel of patient derived xenograft models to enable focused pre-clinical drug development of rationally designed therapies in specific molecular subgroups. We observed unique patterns, including synergies, of drug activity across our molecularly diverse HCC xenografts, pointing to specific therapeutic vulnerabilities for individual tumors. These efforts inform clinical trial designs and catalyze therapeutic development. It also argues for efficient strategic allocation of patients into appropriate enriched clinical trials. Here, we will discuss some of the recent important therapeutic studies in advanced HCC and also some of the potential strategies to optimize clinical therapeutic development moving forward.

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1. Introduction

Hepatocellular carcinoma (HCC) remains a major global health problem [1]. It is the fifth most common cancer in men, seventh in women and the third most common cause of cancer deaths worldwide [2]. In 2008, approximately 749,000 new cases of HCC were diagnosed and 695,000 deaths were attributed to HCC. There is distinct geographical variation with the majority of the cases (85%) occurring in developing countries in East Asia and sub-Saharan Africa and lower incidence rates in Australia, Northern Europe and America [3,4].

The pathogenesis of HCC is composed of a multistep progression involving chronic inflammation, hyperplasia, dysplasia and finally malignant transformation. Cirrhosis is present in 80% to 90% of patients with HCC. The main risk factors for development of HCC are therefore related to the formation and progression of cirrhosis. Chronic hepatitis B (HBV) infection is the predominant etiological agent accounting for approximately half of all cases of HCC. HBV is endemic in high incidence regions across China and Africa. HBV also accounts for a large proportion of HCC cases among Asian Americans. Hepatitis C infection (HCV) confers a 15–20 fold increased risk of HCC and accounts for the majority of cases in Japan, United States and parts of Europe. HCC related to HCV has become the fastest-rising cause of cancer-related death in the United States. Metabolic causes leading to non-alcoholic fatty liver disease are also an increasing concern. The other risk factors for HCC can be classified as toxins

* Corresponding author at: Department of Medical Oncology, 11 Hospital Drive, National Cancer Centre Singapore, Singapore 169610. Tel.: +65 64368000.
E-mail address: dawnchong@gmail.com (D.Q. Chong).

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(aflatoxin B1, alcohol), metabolic diseases (non-alcoholic fatty liver disease, diabetes), hereditary diseases (hemochromatosis) and immune related diseases (autoimmune hepatitis and primary biliary cirrhosis) [5,6].

Despite decades of research in HCC, prognosis still remains poor. Only 20% of the patients with HCC are amenable to curative strategies such as resection, transplantation or local therapy with radiofrequency ablation [7]. Another 20% have multifocal lesions for which locoregional modalities such as transarterial chemoembolization (TACE) [8,9] or selective internal radiotherapy (SIRT) [10–12] can be employed. The majority of patients are not candidates for curative treatment or loco-regional approaches and will receive systemic therapy if they have adequate hepatic reserves and good functional status [7,13]. Due to the underlying liver dysfunction, many patients do not receive any anti-cancer therapy and are palliated with symptom control and best supportive care.

Substantial efforts have been made to molecularly characterize HCC and rationally develop targeted therapeutics in HCC. Unlike other solid tumors, there are no oncogenic addiction loops that have successfully completed the journey from bench to bedside as validated therapeutic targets in HCC [14]. Despite that, only one drug, sorafenib, is FDA approved for the treatment of advanced HCC, achieving modest objective response rates while still conferring an overall survival benefit. In this review, we describe the current landscape of drug development in HCC in light of its molecular heterogeneity, present the available evidence in support of stratified therapy for HCC and discuss potential strategies to accelerate this process by optimizing clinical trials design.

2. Current therapeutic landscape in advanced HCC

2.1. Chemotherapy in HCC

The impact of systemic chemotherapy is limited in HCC patients because of cirrhotic livers and potentially poor hepatic reserves. Specific complications of cirrhosis such as thrombocytopenia also compromise effective delivery of systemic chemotherapy. Several phase II trials with various chemotherapy agents such as doxorubicin, gemcitabine and capecitabine have reported modest results. Among these agents, anthracyclines such as doxorubicin appear to have the most activity, with response rate of 20% and a median survival of 4 months [15–20].

2.2. Combination chemotherapy in HCC

Combination chemotherapy is employed in HCC to obtain a radiological response and can still be employed for quicker palliation. A retrospective multi-center series of 210 patients reported that gemcitabine with oxaliplatin led to an objective response rate of 21% (WHO criteria) and disease control rate of 62%. In addition, 10% of patients had responses that made secondary "curative-intent" surgical therapies possible.

The phase 3 EACH study randomized 371 Asian patients with advanced HCC to open-label FOLFOX4 regimen (5-fluorouracil and leucovorin plus oxaliplatin) or single-agent doxorubicin, crossover was not permitted [21]. Objective response rate (8.2% vs. 2.7%) and disease control rate (52% vs. 32%) were superior with FOLFOX4. The study's pre-specified final analysis, conducted after 266 deaths in the intent-to-treat population, showed a trend toward better median overall survival (the primary end point) among patients treated with FOLFOX4, compared with doxorubicin (6.40 vs. 4.97 months; hazard ratio (HR) 0.79; $p = 0.07$ using a stratified log-rank test). Statistical significance ($p = 0.0425$) was achieved at the post hoc analysis conducted after additional follow-up of 7 months and 305 deaths (HR, 0.79; $p = 0.04$). However, there have been statistical concerns raised regarding the validity of this post-hoc analysis.

The combination of chemotherapy with immunotherapy has also been evaluated. The only randomized phase III study by Yeo et al. reported a response rate of 21% with PIAF (cisplatin, doxorubicin, interferon, and fluorouracil) and a median overall survival of 8.7 months in patients with unresectable HCC. However, PIAF did not result in a significant survival benefit compared to doxorubicin and had significantly more toxicities [22].

2.3. Sorafenib

Sorafenib is the first and only FDA approved drug for use in advanced HCC. It inhibits multiple receptors, namely VEGFR 1–3, PDGFR-B, c-KIT and Fms-related tyrosine kinase-3(FLT-3) [23,24]. Sorafenib has been shown to inhibit angiogenesis, induce apoptosis and inhibit the mTOR pathway in preclinical studies [25]. FDA approval was based on the pivotal phase III Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol (SHARP) trial. Llovet et al. randomized 602 patients (mainly from Europe) with unresectable advanced HCC with Child-Pugh "A" score without prior systemic therapy to sorafenib 400 mg BD ($n = 299$) or placebo ($n = 303$) [26]. Compared to placebo, sorafenib significantly prolonged time to progression (TTP) from a median of 2.8 months to 5.5 months (HR 0.58) and overall survival (OS) from a median of 7.9 months to 10.7 months (HR 0.69; 95% CI 0.55–0.87; $p < 0.001$). This randomized trial clearly established the survival benefit of sorafenib in advanced HCC. Notably, there was no difference in the median time to symptomatic progression (TTSP), a co-primary end-point. A parallel study was performed in 271 Asian patients with advanced HCC by Cheng et al. which also showed a statistically significant improvement of overall survival (HR 0.68; 95% CI 0.50–0.93; $p = 0.014$). However, outcomes in both arms were poorer with a median overall survival of 4.2 months in the placebo arm and 6.5 months with sorafenib therapy respectively. Median time to progression (TTP) was 2.8 months in the sorafenib arm compared to 1.4 months in the placebo arm. Akin to the SHARP study, there was no significant difference in the time to symptomatic progression [27]. The shorter time to progression and median overall survival in the Asian study were postulated to be due to the presence of more unfavorable prognostic factors including higher incidence of hepatitis B infections (73% vs. 12%) and more advanced disease with a higher proportion of extra-hepatic metastasis.

Of note, both trials required Child-Pugh class A score as an inclusion criteria. There are no randomized data regarding efficacy of sorafenib in Child-Pugh B patients. A phase II study by Abou-Alfa that included patients with Child-Pugh B status

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