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Tumour Review

Personalized therapy for hepatocellular carcinoma: Where are we now?

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ABSTRACT

Following the approval of sorafenib, a large number of molecular targeted agents have been tested clinically for advanced hepatocellular carcinoma (HCC), but all have failed to demonstrate significant efficacy in clinical trials. Multiple reasons for this phenomenon have been discussed in the literature, with one reason being the lack of patient selection on the basis of molecular profile in clinical trials. The concept of drug testing in selected populations has been recently suggested by retrospective analyses of HCC clinical trials in which a particular subgroup of patients, either enriched by clinical factors or by tissue biomarkers, derived more benefits from the novel drug. In addition, recent advances in genomic medicine have enhanced the understanding of genetic and epigenetic events occurring in HCC, raising the possibility of personalizing targeted agents in accordance with the genetic make-up of the tumors. The development of 'personalized' treatment for HCC is, however, hindered by the lack of fresh biopsy of advanced HCC, the low incidence of genetic driver mutations in HCC and the tumor heterogeneity. These limitations may be overcome by sequencing cell-free DNA in plasma, frequently known as liquid biopsy, and revolution in the concept of the design of clinical trials. In this review article, we aim to: (1) give a summary of the recent sequencing results of HCC and the related implications for drug development; (2) highlight potential individual targeted agents and existing research on biomarker selection in clinical trials; and (3) discuss future directions, including the potential of liquid biopsy and umbrella clinical trials, to enhance personalized drug testing for HCC.

Introduction

Evolving epidemiology of hepatocellular carcinoma

Globally, hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the seventh in women [1]. The incidence of HCC has reached a plateau in Asia, but has shown an increasing trend in previously low incidence areas such as the US and Europe [2]. Data from the surveillance, epidemiology, and end results program indicate that the age-adjusted incidence rates of HCC have increased from 1.4 per 100,000 in 1975–1977 to 4.8 per 100,000 in 2005–2007 [3]. This pattern can mostly be explained by the infectious etiological link. In Asia, except for Japan, the predominant etiology of HCC is hepatitis B virus (HBV) infection as a result of maternal transmission [4]. With the introduction of HBV vaccination in most Asian countries, the incidence of HCC in adolescents in Asia has shown a decreasing trend, and the incidence in adults is expected to decrease in the next two to three decades [5,6]. The rising incidence of HCC in western countries is the result of an aging population infected with hepatitis C virus (HCV) [7]. Another contributing factor is cirrhosis related to non-alcoholic fatty liver disease (NAFLD). NAFLD is the hepatic manifestation of metabolic syndrome related to interlinked metabolic risk factors [8,9], with a wide clinicopathological spectrum ranging from isolated hepatic steatosis to non-alcoholic steatohepatitis (NASH), which is the more aggressive form of fatty liver disease [10]. With the steadily increasing prevalence of NAFLD and its co-morbidities in a large proportion of the population, NAFLD-associated HCC is a growing health concern [11].

The prognosis for HCC is poor, with a 5-year overall survival (OS) rate of <20% and an estimated number of deaths of nearly 745,000 in 2012 [1,12,13]. The poor outcome is multifactorial, and includes comorbid cirrhosis, late presentation, and the

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Table 1
Published results of key randomized clinical trials of molecular targeted agents after the approval of sorafenib.

Drug	Phase	Number	Median OS (months)	HR (*p* value)	Study
First-line					
Sunitinib	III	530	7.9	1.13 (0.2286)	Cheng et al. [27]
Sorafenib		542	10.2		
Brivanib	III	577	9.5	1.01 (0.3730)	Johnson et al. [122]
Sorafenib		578	9.9		
Linifanib	III	514	9.1	1.046 (ND)	Cainap et al. [123]
Sorafenib		521	9.8		
Dovitinib	II	82	8.0	1.27 (ND)	Cheng et al. [124]
Sorafenib		83	8.5		
Vandetanib (300 mg)	II	19	5.95	0.60 (0.15)	Hsu et al. [125]
Vandetanib (100 mg)		25	5.75	0.44 (0.02)	
Placebo		23	4.27		
Nintedanib	II	62	11.9	0.88 (ND)	Cheng et al. [126]
Sorafenib		31	11.4		
Sorafenib + Erlotinib	III	362	9.5	0.929 (0.408)	Zhu et al. [127]
Sorafenib		358	8.5		
Sorafenib + Doxorubicin	II	47	13.7	0.49 (0.006)	Abou-Alfa et al. [128]
Doxorubicin		49	6.5		
Second-line					
Brivanib	III	263	9.4	0.89 ($p = 0.3307$)	Llovet et al. [28]
Placebo		132	8.2		
Everolimus	III	362	9.4	0.89 ($p = 0.68$)	Zhu et al. [70]
Placebo		184	8.2		
Ramucirumab	III	283	9.2	0.87 (0.14)	Zhu et al. [56]
Placebo		282	7.6		
Axitinib	II	134	12.7	0.870 ($p = 0.211$)	Kang et al. [129]
Placebo		68	9.7		
GC33	II	121	6.8	0.99 (ND)	Yen et al. [130]
Placebo		60	6.7		
Tigatuzumab + Sorafenib	II	54	12.2	ND ($p = 0.659$)	Cheng et al. [131]
Sorafenib		55	8.2		
Tivantinib	II	71	6.6	0.9 ($p = 0.63$)	Santoro et al. [91]
Placebo		36	6.2		

Abbreviations: HR, hazard ratio; OS, overall survival; ND, not determined.

aggressive clinical behavior of the cancer. The first two issues may be partially improved by the recent advancements in antiviral and surveillance strategies. First, the cirrhotic component is expected to be reduced with the increasing use of antiviral therapy for HBV and the availability of effective antiviral treatment for HCV [14–16]. Second, the issue of delayed presentation can be improved by a surveillance program for HCC, which has been shown to identify early-stage disease and improve survival of patients with HCC. Work on risk stratification of HCC development in chronic hepatitis carriers could also help to increase the cost-effectiveness of HCC surveillance by focusing resources on the high-risk population [17–19]. However, even with early diagnosis and improved hepatic function, a sizeable number of HCC patients still have recurrence of the disease after curative treatment, and most patients require systemic therapy at some point after recurrence. For the past two decades, multiple drugs, including cytotoxic and targeted agents, have been tested clinically. Cytotoxic chemotherapy is generally not considered to be a valid option for most patients due to concerns about toxicity and lack of survival benefit in clinical trials [20–22]. In 2007 and 2008, sorafenib was shown to prolong the median OS compared with placebo in two phase III clinical trials [23,24]. As a result, sorafenib became the first systemic targeted agent to be approved by different health authorities for treatment of advanced HCC.

Drug development for HCC from 2007 to 2015

Following the approval of sorafenib, a large number of molecular targeted agents have been tested in clinical trials of HCC. However, none of the trials demonstrated notable results or met the primary endpoint (Table 1). Various reasons have been cited in the literature to explain the failure of these trials, for example, most of the agents tested were tyrosine kinase inhibitors with anti-angiogenic property as the predominant mechanisms. Cumulative evidence has already indicated that anti-angiogenic tyrosine kinase inhibitors have only modest effects in HCC [25], and agents with alternative mechanisms should be developed. Notably, the recent release of clinical data on nivolumab and tremelimumab has motivated clinical research on immunotherapy, especially the checkpoint inhibitor, for HCC [26,27].

Another well-described reason is the presence of comorbid cirrhosis in most patients with HCC, thereby limiting the dose-intensity of treatment and resulting in toxicity-related mortality [28]. Nowadays, it is generally accepted by investigators and industry partners that robust phase I/II study data are required to comprehensively evaluate the toxicity of novel agents in HCC before proceeding to phase III clinical trials. Finally, the prognostication of HCC is more complex than that of other solid tumors because of its heterogeneous clinical prognostic factors. In addition to the conventional factors related to tumor, node, and distant metastases, the outcome of advanced HCC is influenced by variables such as vascular invasion, hepatic function, alpha-fetoprotein (AFP) levels, geographical region, and etiology. Such complexity could render the accrual of a homogeneous study population and estimation of survival extremely difficult during the design of clinical trials for HCC, which is exemplified by the wide range of OS in the placebo arm of a second-line clinical trial [29]. Further, the prognoses of patients undergoing sorafenib treatment are determined by dermatological adverse events and pattern of progression [30,31].