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EDITORIAL

Evolution of systemic therapy of advanced hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) commonly occurs in hepatitis B endemic areas, especially in Asian countries. HCC is highly refractory to cytotoxic chemotherapy. This resistance is partly related to its tumor biology, pharmacokinetic properties, and both intrinsic and acquired drug resistance. There is no convincing evidence thus far that systemic chemotherapy improves overall survival in advanced HCC patients. Other systemic approaches, such as hormonal therapy and immunotherapy, have also disappointing results. Recently, encouraging results have been shown in using sorafenib in the treatment of advanced HCC patients. In this review, we concisely summarize the evolution of developments in the systemic therapy of advanced HCC.

Key words: Advanced hepatocellular carcinoma; Chemotherapy; Doxorubicin; Sorafenib

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth ranking cancer in the world, with more than 80% of cases occurring in Asia[1]. The most common causes of HCC are hepatitis B and C viral infections. Chronic hepatitis B viral infection is prevalent in Asian countries and accounts for most cases of HCC. In contrast, chronic hepatitis C viral infection is more common in Western countries. In recent years, there is an increasing incidence of HCC in Western countries, primarily due to increase in prevalence of hepatitis C viral infection.

Current effective treatments for HCC include liver resection, transplantation, various local ablative and trans-arterial therapies. Surgical resection and liver transplantation are the main curative treatments. Unfortunately, only around 20% patients, mostly diagnosed by regular screening, may benefit from these surgical therapies. Most other patients either present late with advanced tumor or have severe underlying cirrhosis, precluding any surgical or even loco-regional therapies. Previously, these patients can only be palliated by chemotherapy or best supportive treatment alone.

CHEMOTHERAPY TREATMENT OF HCC

HCC is a relatively chemo-resistant tumor and is highly refractory to cytotoxic chemotherapy. This resistance is partly related to its tumor biology, pharmacokinetic properties, and both intrinsic and acquired drug resistance.

In terms of HCC tumor biology, the liver is a defensive organ that responds to the damages in a unique manner. Non-hepatic epithelial cells progress through the cell cycle until they either die or arrest/repair; whereas growth-arrested (i.e. G0) hepatocytes proliferate in response to damage[2,3]. In fact, HCC cells show a higher apoptotic capacity in earlier stages of carcinogenesis. Nonetheless, in advanced stages, they gradually develop the resistance to apoptosis. This anti-apoptotic phenotype is associated with the development and progression of HCC[4]. More importantly, it also partly explains why HCC cells are resistant to cytotoxic chemotherapy. Moreover, p53 mutation is the most commonly encountered alternations in HCC. Both hepatitis viruses and chemicals are implicated in the etiology of p53 mutations during the molecular

Table 1 Pivotal chemotherapy trials in advanced HCC

Chemotherapy	Study	No. of patients	Response rate
Doxorubicin			
Pegylated liposomal doxorubicin	Halm	16	0
Doxorubicin	Johnson	32	44
Doxorubicin, 5-FU, mitomycin C	Al-Idrissi	40	13
Doxorubicin, bleomycin	Ravry	60	16
Doxorubicin, cisplatin	Lee	37	18.9
Doxorubicin, 5-FU, cisplatin, interferon (PIAF)	Yeo	91	20.9
Cisplatin			
Cisplatin	Falkson	35	17
Cisplatin, interferon	Ji	30	13.3
Cisplatin, 5-FU, mitoxantrone	Ikeda	51	27
Gemcitabine			
Gemcitabine	Fuchs	30	0
Gemcitabine	Yang	28	18
Gemcitabine, oxaliplatin	Taieb	21	19
Epirubicin, etoposide			
Epirubicin	Hochster	18	17
Etoposide	Melia	24	13
Epirubicin, etoposide	Bobbio-Pallavicini	36	39
Others			
Mitoxantrone	Lai	20	0
Paclitaxel	Chao	20	0
Irofulven	Falcon-Lizaraso	29	7
Irinotecan	O'Reilly	14	7
Nolatrexed	Stuart	26	8
T138067	Leung	21	10
Capecitabine	Patt	37	11
5-FU, interferon	Patt	28	14

pathogenesis of HCC[5]. As chemotherapeutic agents require p53 to induce apoptosis, tumors with a disruption in p53 pathway are thus resistant to chemotherapy. Furthermore, DNA topoisomerase Ⅱ alpha is over-expressed and up-regulated in HCC cell lines. Since doxorubicin targets DNA topoisomerase Ⅱ, over-expression of the protein in HCC may account for HCC resistance to doxorubicin-based therapy[6]. Regarding its pharmacokinetic properties, the liver plays a pivotal role in the metabolism of both endogenous and exogenous substances inside the body *via* the CYP450 enzyme system[7]. In cirrhotic patients, the total liver mass is reduced, and distortion of the liver architecture leads to significant intra-hepatic shunting and reduced extraction of protein-bound substances. Moreover, cirrhosis also affects the absorption, plasma protein binding, distribution and renal excretion of drugs. Therefore, cirrhosis has a significant impact on the pharmacokinetics of systemic therapy for HCC. Lastly, HCC cells have intrinsic drug resistance mediated by an enhanced cellular drug efflux mechanism, which is usually enacted through the drug transporter family of the ATP-binding cassette proteins that include MDR1, p-glycoprotein and the multidrug resistance protein[8,9]. Moreover, co-expression of p53 and p-glycoprotein also contribute to HCC drug resistance[9].

There is no convincing evidence, thus far, that systemic chemotherapy improves overall survival in advanced HCC patients[10]. Table 1 summarizes the results of pivotal chemotherapy studies of HCC. Single-agent doxorubicin has been shown to produce a response rate of about 10%-15%, but with no proven survival benefit[11]. It has been widely used and regarded as the standard systemic treatment for advanced HCC until recently. Significant grade 3 or 4 toxicities, especially neutropenia, are encountered in patients treated with doxorubicin[12]. Other chemotherapeutic agents, such as epirubicin, cisplatin, 5-fluorouracil, etoposide, and their combinations, have been studied with low response rates and no survival benefit[13]. Similarly, the newer generation of chemotherapeutic agents, such as gemcitabine, irinotecan and pegylated liposomal doxorubicin, also show disappointing results[14,15]. Combination chemotherapy has been employed in the treatment of advanced HCC. Although some of the combination regimes have shown promising activity in phase Ⅱ studies, most of them fail to demonstrate any survival advantage in randomized phase Ⅲ studies[16,17]. Especially, the combination of cisplatin, interferon-alpha-2b, doxorubicin and fluorouracil (PIAF) was under intense investigation at one time. In the phase Ⅱ study, Leung *et al*[18] showed on average 26% partial response, with 4 patients achieving a complete pathological response. Nevertheless, in the phase Ⅲ study, although this combination had achieved higher response rates than other combinations, there was no demonstrable survival benefit and there were considerable toxicities[19]. Recently, a phase Ⅱ study using a combination of gemcitabine and oxaliplatin demonstrated an 18% response rate and 76% of patients had the disease under control[20]. Similarly, another phase Ⅱ study showed a 6% response rate and a 72% disease control rate by employing a 3-wk cycle of capecitabine and oxaliplatin in the treatment of advanced HCC patients[21]. However, as with the results from the PIAF study, these 'promising' data need to be further validated in the ongoing randomized phase Ⅲ trials before they can be employed in routine clinical practice.

HORMONAL THERAPY

Estrogen receptor, progesterone receptor and androgen receptor are expressed in HCC[22,23]. Thus, hormonal agents were used to treat advanced HCC. Among various hormonal agents used for the treatment of advanced HCC patients, tamoxifen was frequently employed in the past, due to its good tolerability and oral administration. However, several prospective randomized controlled trials failed to demonstrate overall survival benefit in treating advanced HCC patients with tamoxifen[24-26]. Moreover, a recent meta-analysis conducted by Nowak *et al*[27] also showed no survival advantage.

IMMUNOTHERAPY OF HCC

Interferon is frequently employed in the treatment of viral hepatitis. However, its role in the treatment of HCC remains controversial. Studies conducted by Lai

et al[28,29] had shown encouraging efficacy with a 30% response rate and overall survival benefit from using a high dose of interferon (2.5×10^7-5.0×10^8 IU/m^2, three times weekly) to treat advanced HCC patients. However, there were significant treatment-related toxicities in patients who received high-dose interferon. On the other hand, when a lower dosage (3×10^6 IU/m^2, three times weekly) of interferon was used instead, there was no demonstrable clinical benefit[30].

SOMATOSTATIN ANALOG TREATMENT

The somatostatin analog octreotide and the long-acting form lanreotide are used in treating HCC, due to the presence of somatostatin receptors in HCC cells[31]. A randomized study, conducted by Kouroumalis *et al*[32], showed survival benefits in employing subcutaneous octreotide in the treatment of advanced HCC patients. Nevertheless, the study conducted by Becker *et al*[33] and Yuen *et al*[34] did not show any survival benefit in using lanreotide in the treatment of advanced HCC patients'.

THALIDOMIDE

Thalidomide was originally introduced in the 1960s as a sedative[35]. It was later re-evaluated for its anti-neoplastic effect in the 1990s. Its mechanism of action is poorly understood and complex, including anti-angiogenesis *via* the inhibition of VEGF, tumor necrosis factor-alpha and modulation of other inflammatory cytokines[36]. It was used in treating advanced HCC patients, mainly due to its anti-angiogenic property. However, single-agent thalidomide[37,38] and its combinations with epirubicin or interferon[39,40] only produced a response rate of 3.1%-6.3% with a median survival of 2.7-6.8 mo. In view of its limited activity and frequent association with treatment-related toxicities, it is now seldom included in the treatment algorithm for advanced HCC patients.

SORAFENIB FOR ADVANCED HCC

Growth factors and related receptors are often overexpressed and/or dysregulated in HCC. Clinical trials indicate that growth factor receptors and their related signalling pathways play important roles in HCC cancer etiology and progression, thus providing rational targets for innovative cancer therapies[41]. Among various growth factor pathways, the activation of the Raf/mitogen-activated protein kinase-extracellular signal-regulated kinase (MAPK) pathway[42,43] plays a pivotal role in promoting the tumor growth. Sorafenib is an oral multi-kinase inhibitor that blocks tumor proliferation by targeting the Raf/MAPK/ERK signaling pathway; it also has anti-angiogenic properties attained by targeting the tyrosine kinase VEGR-2, VEGFR-3 and PDGF receptor β[44]. Recently a large randomized phase Ⅲ study, the SHARP trial[45], was conducted and in this study, 602 patients with biopsy-proven advanced HCC were randomized to receive either sorafenib (400 mg twice daily, $n = 299$) or a placebo ($n = 303$). The results demonstrated a significant improvement in both OS (median 10.7 mo *versus* 7.9 mo) and TTP (median 5.5 mo *versus* 2.8 mo) in the sorafenib group *versus* the placebo group. These results 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. This trial represents the first randomized systemic therapy trial that demonstrates the overall survival benefit of systemic treatment in patients with advanced HCC thus far. Similar to the study design of SHARP study, an Oriental sorafenib study was conducted to investigate the efficacy and tolerability of using single agent sorafenib in treating advanced HCC patients in hepatitis-B endemic Asian population[46]. In this study, the median OS of patient on sorafenib was 6.2 mo which was significantly better than 4.1 mo achieved in patients on placebo ($P = 0.0155$). Again, sorafenib was well-tolerated in Asian patient population. However, the commonest toxicities encountered in Asian patient population were hand-foot skin reactions (10.1%) instead of diarrhea (39%) in the SHARP trial.

CONCLUSION

The management of patients with advanced HCC has been a disappointing issue for decades. The recent development of single agent sorafenib, in the treatment of advanced HCC patients, indeed represents an important advance in this challenging disease. Although these two pivotal studies have demonstrated good activity and tolerability in treating advanced HCC patients with sorafenib, there are still many unresolved issues regarding the optimal use of sorafenib. In particular, most patients enrolled in these two pivotal trials had Child-Pugh A cirrhosis with favorable 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. Moreover, there are currently no reliable clinical parameters or biomarkers which may predict the response to sorafenib. In view of the high cost of sorafenib and potential toxicities associated with sorafenib, reliable biomarkers that can potentially guide the use of sorafenib in the treatment of advanced HCC patients is desperately needed.

Moreover, in the era of targeted therapy, proper patient selection, treatment assessment and endpoints are vital to the success of the clinical trials. This is especially true in HCC, where radiological assessment is difficult, because of poor delineation of the tumor in the liver. Recently, the HCC expert panel meeting recommended adopting a modification of RECIST criteria to assess tumor response[47]. Also, the time to progression was recommended by the panel as the primary endpoint in phase two trials testing targeted therapy in HCC.

The modest improvement, as demonstrated in these two pivotal trials; is still not optimal, as most patients

still have relatively short survival times when compared to patients with other solid tumors, such as colorectal cancer. Therefore, there is a need for researchers to unravel more of the underlying hepato-carcinogenesis mechanism and key molecular targets for therapeutic intervention. Moreover, another future focus will be on how to best combine the other targeting agents or chemotherapeutic agents in order to incrementally improve the survival of advanced HCC patients.

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