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Key research issues in the management of hepatocellular carcinoma

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Abstract Hepatocellular carcinoma (HCC) is an extremely diverse and heterogeneous disease and improving patient outcome is a difficult undertaking. While many therapeutic options exist, few have been subjected to rigorous study, so patient benefit is uncertain. Comparative trials need to be performed to determine the value of these and, of course, newer treatments. However, there are numerous challenges to the design and conduct of such studies. While stratification parameters are important in most clinical trials, they are particularly critical when studying HCC. The cancer staging of HCC must reflect prognosis and, therefore, must include parameters of liver disease. This is because the underlying hepatic dysfunction may often determine how long patients survive and confuse the interpretation of anti-HCC treatment trials. Two new staging paradigms—Cancer of the Liver Italian Program (CLIP) and Chinese University Prognostic Index (CUPI)—have been developed, and these need to be validated. The role of the many different treatment options must be determined. However, the diverse nature of presentation of HCC and the proliferation of many routine procedures—such as chemoembolization or radiofrequency ablation—make controlled trials nearly impossible. Even drug development is a special circumstance, because HCC patients with underlying liver disease may need different dosing regimens and schedules compared to other cancer patients. This makes clinical trial design more cumbersome and the risks of participating in clinical trials for HCC greater. The immense unique challenges of this disease make it imperative for investigators to identify the most promising agents for HCC. At the same time, all patients with HCC should, if possible, be treated on well-designed clinical trials.

Keywords Hepatocellular carcinoma · Trial design · Liver dysfunction

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Introduction

Hepatocellular carcinoma (HCC) is a disease that generates a great deal of research interest. It is a common malignancy worldwide that almost always has an underlying viral disease as its cause. It has a relatively predictable time course and has been the subject of numerous innovative approaches using the latest technology. Nonetheless, while our understanding of the molecular pathophysiology of the disease has grown dramatically over the past decade [2], progress in the prevention and management of this disease has been slow.

The use of hepatitis B vaccination in newborns in Taiwan has all but eliminated childhood HCC there [6], but there have been few if any other significant advances in the management of the disease. There is no evidence that surveillance of patients known to be at risk for HCC improves long-term outcome [18].

Once the disease develops, there are many therapeutic approaches. These options range from percutaneous ablative techniques for localized tumors to aggressive, combination chemotherapy for patients with advanced cancer. For all of these treatment options, however, fewer than 30% of patients with localized HCC are cured [13] and the median survival time for patients with unresectable HCC is a matter of months. The absence of a satisfactory standard treatment and poor prognosis would appear to make HCC patients prime candidates for many of the newer biological therapies being studied, and yet few such agents are being tested in the HCC population.

Why has progress been so slow and why is the research lagging? The answer may be as simple as the fact that HCC is almost always two diseases in one: underlying liver disease and cancer. The presence of cirrhosis may be as or more important than the tumor/node/metastasis (TNM) stage of the cancer in terms of predicting prognosis. Also, liver dysfunction may lead to unpredictable pharmacokinetics or drug disposition, so that treatments may be more toxic to patients with HCC than to those with normal liver function or others included in phase I trials. Such concerns make drug development in HCC risky, limiting the enthusiasm of investigators to test new and promising therapies in patients with HCC.

Furthermore, while the incidence of HCC is increasing in the USA and Europe as a result of chronic hepatitis C infection [8], it is still an unusual diagnosis. The advanced stage and compromised liver function of this relatively small population of HCC patients in the West make clinical trials difficult to complete outside of Asia, where HCC is endemic.

For these reasons, the major challenges to advancing the management of HCC could be listed as follows:

1. How do we stage patients with HCC to account for the extent of underlying liver disease, and then apply this to clinical trials in terms of stratification parameters?
2. How do we design clinical trials to test old or new therapies in HCC?
3. Can we find new agents—biological or other—that target HCC and that can be developed expeditiously?

Staging HCC: TNM is not enough

The conventional TNM staging system for HCC is inadequate. TNM staging is limited by the need to obtain pathologic information, while image-based tumor assessment can be misleading given the difficulty in visualizing HCCs in the cirrhotic liver [7]. Also, factors such as the extent of hepatitis, the etiology of the underlying liver disease, measures of hepatic reserve, and the tumor extension into major or minor vascular structures need to be incorporated into any scheme designed to stratify patients with HCC. It is only with the incorporation of such prognostic factors that clinical trial results can be interpreted and generalized to other patients.

Historically, surgeons and hepatologists divide patients with liver disease into three prognostic categories of the Child-Pugh score [17]. This classification scheme, graded A through C, incorporates the presence or absence of surrogate markers of liver disease such as encephalopathy, ascites, low albumin and increased total bilirubin or prothrombin time to approximate surgical risk and prognosis. This system remains relevant for liver transplantation algorithms and for the interpretation of therapies for chronic liver disease.

Okuda et al. expanded the Child-Pugh score in developing a staging system applicable to patients with HCC [15]. Okuda et al. used three of the Child-Pugh markers—presence or absence of ascites, serum albumin, and total bilirubin—and an estimate of the amount of liver replacement by tumor to create three stages. Then, in a retrospective analysis of 850 HCC patients treated with a variety of interventions, this staging system was validated. Until recently, this convention has governed the design, reporting and interpretation of most studies in patients with HCC.

Unfortunately, the method of Okuda et al. has limited sensitivity. The stages are broad and the ability to distinguish patients within categories difficult. Okuda staging may predict a patient's suitability for a curative operation, but it cannot distinguish the majority of patients, most with advanced disease or major vascular involvement who would be lumped into the other categories, but who may have entirely different natural histories.

This dilemma has led to the description of three new HCC staging systems. The CLIP (Cancer of the Liver Italian Program) uses the Child-Pugh score in a formula that includes points for tumor morphology, alpha-fetoprotein level and the presence or absence of portal vein thrombosis [3]. It has been validated in an Italian population of HCC patients (mostly due to hepatitis C) [4] and appears to be more sensitive than the Okuda system, essentially creating six prognostic groupings (CLIP score 0–5). Investigators in Hong Kong have defined a staging system based on their experience in patients with HCC. This system, called the CUPI (Chinese University Prognostic Index) [12], assigns points for TNM stage, and the presence or absence of symptoms or ascites. Alpha-fetoprotein level, total bilirubin and alkaline phosphatase are also incorporated into this model. An even simpler model has been proposed by investigators in Singapore, who assign prognostic points based on just three simple clinical parameters: alpha-fetoprotein level, the presence of ascites, and performance status [19]. This model also appears to stratify patients for survival.

Whether the CLIP, CUPI, Singapore model or some other system is the optimal staging scheme is uncertain. The CLIP, developed in Italy, largely reflects a population of patients who do not have hepatitis B as an underlying etiology for liver disease, while the CUPI and Singapore models were developed in a mostly hepatitis B dataset. These scores still need validation across a range of HCC patients, and one system may be preferable to another depending upon the setting. For example, a clinical trial studying a regional strategy might well exclude patients with portal vein thrombosis and advanced cirrhosis, making the CLIP scoring system less useful because of the weighting those factors have in that system. But an accurate means of stratification will be critical if results from one population of HCC patients are to be applied to another.

Drug development in patients with liver dysfunction

The complexities of developing drugs for use in patients with liver disease are obvious. Agents often require a metabolic intervention by the liver, either to activate a prodrug or to inactivate a toxic metabolite. This function will depend on both the integrity of the hepatocytes and biliary tract as well as blood flow to the liver. In either circumstance, cirrhosis of the liver or liver dysfunction may profoundly alter the pharmacokinetics of an agent and make clinical trials difficult to implement and/or interpret.

For example, doxorubicin is metabolized by the liver. By historical practice, patients with elevations of total bilirubin receive lesser (if any) doses of doxorubicin [1]. Thrombocytopenia, a common finding in patients with cirrhosis of the liver, also dictates dose reduction of doxorubicin. Studies assessing the efficacy and toxicity of doxorubicin in HCC have been discouraging [9], perhaps partly reflecting the dose reduction schema recommended for the agent and the use of subtherapeutic doses.

Phase I studies have been performed that attempt to address the issue of drug dosing in patients with liver dysfunction (as well as for patients with renal insufficiency). Parameters for numerous chemotherapeutics, including the taxanes [20] and gemcitabine [21], have been published. However, the challenge—finding appropriate surrogates for liver disease and making safe dosing recommendations—remains. Because of their small size and design, phase I studies are fraught with potential problems, raising the chance that the wrong dose of a chemotherapeutic—too much or too little—will be used in trials for HCC.

One solution is to design therapeutic trials for HCC with a phase I run-in component, testing the dose of an agent as used in other patients in a dose-escalation scheme for patients with HCC. This adds months to HCC study completion and complicates the development pathway for promising agents in the disease. Newer clinical trial methodologies, perhaps employing stratification parameters as described above with an eye toward identifying predictors of drug toxicity, are imperative for the more rapid accrual of patients to therapeutic trials for HCC.

Designing clinical trials in HCC

Given that the only accepted "standard" therapy for HCC—resection—can be questioned, it is safe to say that no treatment stands unchallenged. There are many clinical research issues, but one list of four important research questions is:

1. Should we resect or perform liver transplantation for patients with isolated HCC?
2. Do local-regional therapies improve survival?
3. Is there a chemotherapy "standard", and how do we find something better?
4. Can we bridge patients with early HCC to liver transplantation?There are data reflecting on each of these questions, but the retrospective nature of most analyses make conclusions difficult.

For example, should we perform liver resection or liver transplantation? One analysis suggested that transplantation leads to better long-term results [16] since it rids patients of both the HCC risk and the cirrhosis of the liver. Yet other retrospective series have concluded the opposite [5]. Similarly, numerous phase II reports suggest efficacy and infer a benefit to local therapies—chemoembolization, radiofrequency ablation—for HCC. However, results from controlled studies are not convincing. For every positive report of a survival advantage for chemoembolization [14], there is at least one contrary finding [10]. Which of these modalities is the right one for a patient with a small HCC awaiting liver transplantation?

As to studying systemic chemotherapies, trial design may be even more critical. The standard drug development approach is doomed to failure. As stated above, there is the issue of choosing a dose of the agent, a decision that needs to be made in the same patient population, those patients with HCC and liver disease. And once a dose is selected, the tendency to move into a conventional, phase II trial is inevitable, but ill-advised. For starters, what level of response would be significant? Is a 32% response rate, as has been seen in a single trial with doxorubicin [11], the benchmark? And what of alpha-fetoprotein responses, minor responses and stable disease, as opposed to new portal vein thrombosis? All of these scenarios are relevant and need to be accounted for, as does the patient whose tumor may necrose but who progresses into hepatic failure.

What is the solution to these problems? Well-designed, randomized trials need to be conducted across all stages of this disease. These trials need rigorously to define patient populations. Clear stratification parameters for liver dysfunction need to be incorporated, trying to ensure that balance exists between patients on different arms. The trial designs also need to incorporate stratifications for the etiology of underlying liver disease, since the natural history of hepatitis B or C virus liver disease may be highly variable. Depending upon the modality, such studies could be powered to show a survival advantage or merely a suggestion of activity of a new, perhaps less-toxic, agent.

Which new treatments have the best chance of having an impact on HCC?

Recognizing the complexity of clinical trial design for HCC and given the relative paucity of patients in the USA and Europe with the disease, it is useful (although purely speculative) to handicap the list of new treatments

to predict which is the likeliest to lead to advances in HCC. There are at least two conventional chemotherapeutic agents in clinical trials for HCC. Nolatrexed (Thymitaq), a rationally designed inhibitor of thymidylate synthase, is in phase III studies worldwide. Another compound, T-67 from Tularik, is also in phase III trials. Each is being tested based on the serendipitous observation of clinical responses in HCC patients participating in the early developmental phases of drug development.

Numerous regional approaches are also being evaluated. These include ablative techniques, attempts to enhance local drug delivery (such as magnetic targeted carrier bound to doxorubicin, MTC-Dox, in worldwide phase III trials) or the systemic administration of prodrugs that might be preferentially activated by hepatic enzymes. Ultimately, each would need to be compared to a standard comparison arm to determine if any advantage for the therapies exists. In the future, these regional delivery methods with their specific targeting ability may best be applied to some of the novel agents.

Conclusion

The challenges to conducting clinical research in HCC are numerous. Accounting for the underlying liver disease, both to determine efficacy and to safeguard against unexpected toxicity, requires unique clinical trial designs. While many of the newer agents may, in fact, have potential activity in the disease, the obstacles to testing them in HCC may impede progress in this disease.

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