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REVIEW

Systemic treatment in hepatocellular carcinoma; 'A small step for man...'

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ABSTRACT

Hepatocellular carcinoma (HCC) is the third most common cause of cancer mortality worldwide. In localised disease, orthotopic liver transplantation, surgical resection or local ablations are the mainstay of treatment. In unresectable or metastatic HCC, systemic therapy has unfortunately yielded disappointing results and therefore until recently was generally considered to be ineffective. Most patients with HCC have an underlying liver disease and many drugs may exacerbate the underlying liver disease. Recently, two randomised phase III trials with sorafenib in patients with advanced or metastatic HCC have shown a significant increase in progression free and overall survival of approximately two months, which is an absolute novum for this disease. Sorafenib is therefore now considered a viable treatment option in patients with unresectable or metastatic HCC, a good performance status and Child-Pugh A liver cirrhosis. Despite this very promising result, of major concern is the treatment-related toxicity as observed in these and other trials by sorafenib treatment. However, the important first significant survival benefit by systemic treatment has generated hope for the development of new treatment strategies which will be more efficacious, have favourable toxicity profiles and will further extend survival of this still highly lethal disease.

KEYWORDS

Advanced hepatocellular carcinoma, sorafenib, therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the third cause of cancer-related mortality. While the incidence of HCC is high in Asia and parts of Africa, in the Western world its incidence is low although increasing.[1-3] As an example, the yearly incidence of HCC in the Netherlands is an average of 250 patients, and between 1989 and 2000 this figure has not changed.[4]

Cirrhosis is the main risk factor underlying HCC, and there is a clear association between chronic infections with hepatitis C virus, hepatitis B virus, excessive alcohol consumption, cirrhosis and HCC. However, HCC also occurs in a noncirrhotic liver. Surgical resection, local ablation and liver transplantation are the mainstay of treatment of localised HCC. Unfortunately, only 25% of patients will present with localised disease and can receive such a potentially curative therapy.[5,6] In patients unable to receive any of these alternatives, systemic therapy was generally considered to be ineffective.[7] Recently, results of two randomised phase III trials have been published showing efficacy of sorafenib in advanced HCC. In this review we will give a brief overview of the currently applied local treatment options for HCC and will discuss data of the past and present systemic treatment for HCC. As nowadays various different treatment options for patients with HCC can and should be considered, it is the conviction of the authors that patients should be treated in experienced hepatobiliary centres with the availability of a multidisciplinary input.

TREATMENT OF LOCALISED HCC

Partial liver resection

Partial liver resection is the treatment of choice for HCC in a noncirrhotic liver. Irrespective of the usual large tumour size (8 to 10 cm), five-year survival rates exceeding 50% have been described.[8] Among patients with underlying cirrhosis, strict selection criteria are required to avoid treatment-related complications. While in the 1970s a cirrhotic liver was considered a contraindication for resection, partial hepatic resection is now a safe and viable option with a perioperative mortality of less than 5%. Currently only the presence of extrahepatic disease, lack of sufficient hepatic functional reserve (Child-Pugh B or C cirrhosis), multi-focal hepatic disease, and main portal vein involvement and of course severe comorbidity are still considered contraindications for partial liver resection. Studies of surgical resection in HCC over the past ten years have demonstrated five-year survival rates of 25 to 92%.[5,9] This wide range is primarily explained by differences in patient selection. Severity of underlying liver disease, number and size of HCC nodules and the presence of portal hypertension are important prognostic factors. Careful selection of patients with a single HCC <5 cm, with a preserved liver function without portal hypertension yields five-year survival rates of 70%.[7]

Orthotopic liver transplantation

Thomas E. Starzl performed the first liver transplantation in 1963. Since then, orthotopic liver transplantation (OLT) has become the worldwide mainstay for patients with resectable HCC. In theory, total hepatectomy followed by OLT is the optimal curative approach, as this procedure removes the 'precancerous' liver and all microscopic disease at the time of resection. Worldwide, the so-called 'Milan criteria' are the most accepted selection criteria for OLT in HCC.[10] In the decisive study by Mazzaferro *et al.*, patients with a relatively limited HCC (1 nodule <5 cm, 3 nodules < 3 cm) had a comparable outcome to transplanted patients not suffering from HCC (four-year survival of 75%). Some centres consider these criteria to be too restrictive. Yao *et al.* reported the outcome of 70 patients with HCC undergoing OLT and found that patients with a single lesion ≤6.5 cm, two to three nodules with the largest ≤4.5 cm or a total tumour diameter ≤8 cm had a 75% five-year survival.[11]

Recent studies have confirmed the outcome of these expanded criteria, the University of California, San Francisco (UCSF) criteria; comparing the Milan and UCSF criteria, no statistical difference in five-year post-transplant survival was found.[12] Future studies will have to prove feasibility and acceptability of these expanded criteria.

Microscopic vascular tumour invasion is the main prognostic factor. Unfortunately, this cannot always be assessed reliably in the preoperative situation. For patients with HCC in decompensated cirrhosis, OLT remains the only curative option. It is obvious that the presence of extrahepatic disease is an absolute contraindication for OLT.

Local ablative therapies

Local ablation techniques are accepted alternative therapies for unresectable HCC. Interstitial laser coagulation, cryotherapy, microwave ablation, percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) are the most frequently used approaches. Five-year survival rates up to 70% have been described.[13] Underlying liver disease and number and size of HCC lesions are the main prognostic factors. An adequately performed RFA is now considered the preferred local ablative treatment. When tumours are located close to bile ducts or large vessels, PEI remains a valuable option. Recent studies comparing the efficacy of surgery and local ablative therapies in small HCC have clearly demonstrated that a well-performed local ablation yields similar survival rates and less morbidity compared with surgery.[14-16] Based upon these reported success rates, RFA and PEI should be classified as potentially curative. In the future, local ablative therapies will probably become the mainstay of treatment of small tumours (3 cm).

Transarterial chemoembolisation

Transarterial chemoembolisation (TACE) is an accepted alternative therapy for unresectable HCC without extraheptical spread. Meta-analysis reported a survival benefit after TACE especially in patients with a decompensated liver function. Therefore, TACE might be therapy of choice in careful selected patients.[13]

TREATMENT OF ADVANCED HCC

As mentioned before, until recently no proven or standard systemic therapy for advanced HCC could be defined. Numerous small phase II studies with hormonal treatment, immunotherapy or cytotoxic chemotherapy all yielded disappointing response rates and no significant effects on disease-free and overall survival. Based upon the successes of so-called 'targeted' therapies in other solid tumours, renewed interest in possibilities for such systemic therapy in HCC has emerged.

Several preclinical studies have suggested that some small molecule tyrosine kinase inhibitors (TKI) as well as monoclonal antibodies inhibit important signalling pathways in tumour cells and can inhibit angiogenesis in HCC. Using this evidence, a number of nonrandomised phase II trials have been performed to investigate these agents, either alone or in combination with chemotherapy in patients with HCC (*table 1*).[17-22]

Table 1. *Phase II trials with targeted agents in hepatocellular carcinoma*

Author (year)	n	Agent/dose	PR (%)	TTP (months)	MS (months)
Philip (2005)[17]	38	Erlotinib 150 mg once daily	8	3.2	13
Abou-Alfa (2006)[18]	137	Sorafenib 400 mg twice daily	2.2	4.2	9.2
Zhu (2006)[19]	33	Gemcitabine/oxaliplatin + bevacizumab	20	5.3	9.6
Louafi (2007)[20]	44	GEMOX + cetuximab	23	6.3	11.5
Zhu (2008)[21]	34	Sunitinib 37.5 mg once daily	3	4	9.9
Siegel (2008)[22]	46	Bevacizumab 10/5	13	6.5	12.4

PR = partial response; TTP = time to progression; MS = median overall survival.

Sorafenib is such a small molecule tyrosine kinase inhibitor. It inhibits signalling pathways relevant for both tumour cell proliferation (C-RAF, B-RAF, V600E B-RAF, c-KIT and FLT-3) and angiogenesis (C-RAF, VEGFR-2, VEGFR-3 and PDGFR-β). In preclinical studies sorafenib was able to inhibit tumour growth in several human tumour xenograft models.[23] Based upon results obtained in smaller phase I and II trials, two large randomised phase III trials have been performed (*table 2*).

RANDOMISED PHASE III TRIAL OF SORAFENIB IN ADVANCED HCC

The largest randomised phase III trial in HCC (SHARP trial) was performed in a Western population.[24] Patients were randomly assigned to receive continuous oral treatment with 400 mg sorafenib twice daily or matching placebo in combination with best supportive care. Treatment was continued until disease progression or presence of unacceptable drug-related adverse effects.
With respect to demographic characteristics, no significant differences between the two groups were observed, whereas approximately half of the patients had not been previously treated, and locoregional therapy (TACE, PEI and/or RFA) had failed in the remaining patients. Important outcomes for clinical evaluation are summarised in *table 3*. Although no significant difference in tumour response was observed, both progression-free survival and overall survival increased significantly following exposure to sorafenib. The percentage of patients who discontinued dosing was 13 in the placebo group and 32 in the sorafenib group. In the placebo group 101 patients (33%) and in the sorafenib group 154 patients (52%) interrupted the treatment because of drug-related adverse effects. Median duration of treatment was 23 weeks in the sorafenib group and 19 weeks in the placebo group. Drug-related adverse events (all grades) were reported in 80% of the patients in the sorafenib group and in 52% of patients in the placebo group. Primary drug-related adverse events reported were dermatological (constitutional and hand-foot skin reaction) and gastrointestinal (diarrhoea, nausea). A second randomised phase III trial was performed in Asian-Pacific patients. In this study, patients were in a 2:1 setting assigned to receive either sorafenib 400 mg twice daily or matching placebo.[25] Treatment was continued until disease progression or the

Table 2. *Randomised phase III trials of sorafenib and hepatocellular carcinoma*

Patient characteristics	Llovet et al.[24]		Cheng et al.[25]	
	Sorafenib n=299	Placebo n=303	Sorafenib n=150	Placebo n=76
Median age (years)	64.9±11.2	66.3±10.2	51 (23-86)	52 (25-79)
Child-Pugh class A	95%	98 %	97 %	97 %
ECOG-PS:				
0	54%	54%	25%	28%
1	38%	39%	69%	67%
2	8%	7%	5%	5%
Macroscopic vascular invasion	36%	41%	64%	66%
Extrahepatic spread	53%	50%	36%	34%
Macroscopic vascular invasion, extrahepatic spread, or both	70%	70%	-	-
Underlying hepatitis B	19%	18%	71%	78%
Underlying hepatitis C	29%	27%	11%	4%
Alcoholic cirrhosis	26%	26%	-	-

ECOG-PS = Eastern Cooperative Oncology Group - performance status.

Table 3. *Outcome randomised phase III trials of sorafenib and hepatocellular carcinoma*

Outcome	Llovet et al.[24]		Cheng et al.[25]	
	Sorafenib n=226	Placebo n=242	Sorafenib n=150	Placebo n=76
Progression-free survival (months)*	5.2	2.8	2.8	1.4
Overall survival (months)*	10.7	7.9	6.5	4.2
Response rate (%)	2	1	3	1
Drug-related adverse events grade 3/4 (%)	35	15	26	2

***Median.**

occurrence of unacceptable drug-related adverse effects. With respect to the demographic characteristics no relevant differences between the two study groups were found. When comparing the population enrolled in this trial with that enrolled in the SHARP trial, the most striking differences are the predominant cause of underlying liver disease (predominantly hepatitis B infection in the Asian-Pacific population as opposed to hepatitis C infection in the Western population) and the median age, which is much lower in the Asian-Pacific population.

Important outcomes of this trial are summarised in *table 3*. Comparable with the results obtained in the SHARP trial, progression-free survival almost doubled and overall survival increased significantly. In both studies, these favourable results were obtained while the response rate was remarkably low.

Primary drug-related adverse events reported were dermatological (constitutional and hand-foot skin reaction) and gastrointestinal, and also these observations were strikingly remarkable in the two studies reviewed. The toxicity of sorafenib is a serious problem. Approximately 50% of patients have to interrupt or stop treatment because of sorafenib-induced toxicity. Toxicity of this type of agent was initially not expected and is of concern for combination treatment strategies.[26] Optimal clinical management of these side effects is of high priority to optimise treatment intensity for patients and thereby treatment outcome.

UNRESECTABLE OR METASTATIC HCC; CURRENT CLINICAL PRACTICE.

For patients diagnosed with advanced or metastatic HCC, sorafenib is currently the only treatment option that has demonstrated survival benefit in randomised controlled trials. Of note here is that these trials almost exclusively enrolled patients in a favourable clinical and biochemical condition, (Child-Pugh liver function class A and ECOG-PS 0 or 1). In the limited number of patients enrolled in both trials suffering from more severe underlying liver disease, e.g. Child-Pugh B, the response rate to sorafenib seemed to be comparable to that observed in patients with Child-Pugh A which, as mentioned before, was very low. The effects of sorafenib on progression free or overall survival of patients in Child-Pugh B was not reported separately in the two trials and future studies must therefore address this issue in more detail, and until results are known, patients with advanced or metastatic HCC and Child-Pugh B (and especially C) liver cirrhosis should not be treated systemically with either sorafenib or any other agent outside the setting of clinical studies. Fortunately, a large number of these clinical studies are ongoing or will be initiated in the near future, giving patients an increasing opportunity to become exposed to new and potentially effective antitumour agents.

TACE is a worldwide-accepted treatment for unresectable HCC without extrahepatic spread. Survival seems to increase after TACE, especially in patients with a compensated liver function.[13] At the moment TACE is the standard treatment for patients with intermediate BCLC staging (patients without extra-hepatic disease and limited HCCs in the liver).[27] Whether the addition of sorafenib to TACE could be beneficial to these patients is currently explored in clinical trials.

SORAFENIB AND HCC: THE FUTURE

The positive results of sorafenib in advanced or metastatic HCC open new avenues for this agent in less advanced stages of HCC. Trials exploring the role of sorafenib as adjuvant treatment following such curative treatment options as resection and RFA are currently ongoing.[28]

As the response rate of HCC to sorafenib is only very low (2 to 3%), it is very unlikely that sorafenib could turn out to be effective as induction treatment in an attempt to render an unresectable HCC to a resectable disease. It cannot be excluded that this obviously disappointing response rate depends on drug dose, and therefore increasing the dose might increase the response rate in HCC; of note here is that these observations have been made in advanced renal cell carcinoma.[29] Current trials are comparing sorafenib with chemotherapies or other targeted agents in order to improve outcome of unresectable HCC.[30,31] Trials combining sorafenib with RFA or TACE will be initiated soon, partly based on promising data on such combinations (sorafenib and RFA) in mice.[32]

CONCLUSION

HCC is a complex disease that merits a multidisciplinary approach. In resectable and irresectable and/or metastatic disease progress has been made with the treatment by the introduction of new treatment modalities. Based upon these results, efforts to improve outcome even further are currently underway, and hopefully the breakthrough that has been observed in recent years will turn out to be the beginning of new era where HCC is considered a treatable and increasingly curable disease.

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