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Emerging strategies in the treatment of advanced hepatocellular carcinoma: the role of targeted therapies.

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Abstract

Hepatocellular cancer (HCC) is the fifth most common cause of cancer worldwide and its incidence is increasing due to the dissemination of hepatitis B and C virus infection. Surgical resection and liver transplantation are considered the only cures for HCC, but benefit approximately 10-15% of patients. In addition, radiofrequency ablation may be potentially curative for patients' with small HCC. Some patients with irresectable disease confined to the liver may benefit from embolisation or chemoembolisation. In the presence of disease not amenable to loco-regional therapy median survival is only a few months. Current systemic therapy with cytotoxic chemotherapy induces relatively few responses and has no clear survival benefit.

Current interest is focussed on the potential role of targeted therapies based on the key aspects of molecular pathogenesis of HCC, most notably sorafenib, an oral multikinase inhibitor. Recent developments discussed in this article demonstrate the potential benefits of this drug which seems destined to become first-line therapy for advanced HCC.

Introduction

Hepatocellular carcinoma is the fifth most common malignancy worldwide, with approximately 500,000 new cases per year and more than 600,00 deaths annually[1]. Approximately 80% of cases arise in Asia and Africa mainly due to chronic hepatitis B virus (HBV) infection. The incidence of HCC is rising in the United States and Europe because of the increased incidence of hepatitis C (HCV) infection [2]. China has the highest mortality rate for both men and women reflecting the prevalence of HBV infection [3]. HCC is now the leading cause of death in Europe in patients with cirrhosis [4]. As such HCC is a major cause of morbidity and mortality worldwide.

Treatment Options

Surgical and loco-regional

Five year relative survival rates are less than 10% [3]. The only curative treatments for HCC are surgical resection and liver transplantation but only benefit approximately 25% [1].

Surgical resection is only suitable for patients with well preserved liver function and no portal hypertension. Five-year survival following resection is 15-39% [5]. In well selected patients, the 5 year survival rates have approached 50% in a number of large series [6]. Liver transplantation has become the preferred treatment for early stage HCC in cirrhotic patients with 5- year survival rates of 70-80% and tumour recurrence rates of only 10% [7-9].

Treatment options for unresectable disease include locoregional therapy [10, 11] and systemic therapies [12]. Thus far transarterial embolisation (TACE) has been the only locoregional therapy to demonstrate a survival advantage and it is the treatment of choice for intermediate stage HCC (tumour greater than 4cm or multiple lesions in the liver) [6, 10]. Based on this evidence TACE became the standard first-line non-curative therapy for non-surgical/multifocal HCC. Nonetheless, treatment is associated with toxicity and mortality. There is heterogeneity in practice in respect of the embolic particle, lipiodol use, and type of chemotherapy and frequency of administration. The chemotherapy used by a particular unit is often determined by which drug the physicians and radiologists have experience with and are comfortable using. Doses used are often extrapolated from previous experience and what is thought to be 'safe'. Treatment schedules have not necessarily taken into account the projected oncologic behaviour of the tumour.

Studies with TACE have been undertaken in patients with intermediate stage HCC with disease confined to the liver, no main portal vein involvement and good performance status. In contrast studies with systemic therapy, including sorafenib, have been undertaken in patients with advanced HCC not suitable for treatment with TACE. There is a clear rationale for evaluating the combination of TACE in combination with the novel targeted agent sorafenib to evaluate whether this may improve the outcome for patients with intermediate stage disease. TACE

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3 results in increased levels of vascular endothelial growth factor (VEGF), a key driver of
4 angiogenesis increase. These increased levels are associated with increased rate of metastasis
5 and shorter survival. In addition, the Raf/Mek/Erk pathway is important in the development of
6 HCC. Sorafenib as discussed below is an inhibitor of both these pathways. The TACE-2 trial,
7 co-ordinated by the National Cancer Research Network, is now underway to evaluate the
8 addition of sorafenib to TACE.
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20 Systemic Therapies

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22 For patients presenting with disease not amenable to locoregional therapy many will require
23 palliative care alone. However, patients with well preserved liver synthetic function may benefit
24 from systemic chemotherapy. Response rates to single agent cytotoxic chemotherapy range
25 between 0-20% with anthracyclines such as doxorubicin yielding the best response rates of up to
26 20% [13] but with no definite survival benefit. Lai *et al* conducted a randomised trial of
27 adriamycin versus no treatment in advanced HCC in 60 and 46 patients respectively [14]. The
28 median survival rate was 10.6 versus 7.5 weeks respectively ($p=0.036$) however a 25% fatal
29 complication rate due to septicaemia and cardiotoxicity in the treated arm lead the authors to
30 conclude that adriamycin could not be recommended as an ideal drug of choice for advanced
31 HCC. Newer agent cytotoxics have not shown any better responses and have sometimes shown
32 lesser activity.
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43 Nilotrexed is a novel thymidylate synthase inhibitor and has demonstrated limited activity in
44 advanced HCC [15, 16]. A subsequent phase III trial compared the use of nilotrexed versus
45 doxorubicin in unresectable HCC[17]. Median overall survival was 22.3 weeks for nilotrexed
46 versus 32.3 weeks for Doxorubicin ($p=0.0068$) and the hazard ratio was 0.753 in favour of
47 doxorubicin. This was the largest randomised controlled trial using doxorubicin as the control
48 arm and whilst no benefit was demonstrated for the use of nilotrexed, the higher than expected
49 survival rates in both treatment groups may relate to the advances in the management of HCC
50 including better supportive therapies, such as growth factors and greater expertise in the
51 treatment of patients with cirrhosis
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A variety of combination chemotherapy regimens has been studied in advanced HCC. Combination chemotherapy with doxorubicin, cisplatin and 5-fluorouracil with or without interferon [18, 19] have increased response rates modestly (13-39%) but with no clear impact on survival. Taieb *et al* examined the combination of gemcitabine and oxaliplatin (GEMOX) in advanced HCC and demonstrated a 19% clinical response rate and an acceptable toxicity profile [20]

Most regimens have not been validated in randomised trials and therefore their clinical significance is uncertain. In addition combination regimens are often associated with greater toxicities when compared with single agent. In one of the few randomised studies undertaken Yeo *et al* compared doxorubicin with cisplatin/ interferon α -2b/ doxorubicin and 5- fluorouracil in unresectable HCC. Response rates were 10.5% versus 20.9% respectively with a non-statistically significant median survival advantage of 6.83 versus 8.67 months ($p= 0.83$)[19]. However the combination regimen was associated with increased treatment related toxicity over the single agent regimen and therefore its clinical application is limited. In conclusion, although doxorubicin or doxorubicin-based combination therapies are widely used there is no regimen that can be clearly defined as the standard for treating advanced HCC.

These disappointing results can be partially explained by the fact that HCC cells are relatively well differentiated and carry several mechanisms of drug resistance. HCC cells usually contain high levels of dihydropyrimidine dehydrogenase that makes them resistant to 5-fluorouracil [21]. HCC cells also over-express the multidrug resistance gene(MDR1) [22] and the gene product P-glycoprotein [23]. This explains for example the total resistance to paclitaxel [24], which is a P-glycoprotein substrate.

In addition, cirrhosis can have a profound impact on anticancer drug therapy. It not only decreases drug metabolising enzyme activity, but also alters the absorption, plasma protein binding, distribution, and renal excretion of drugs. Intra-hepatic shunts produced during cirrhosis allow drugs to be routed around hepatocytes, thus decreasing their first-pass extraction [25]. However, all routes of hepatic metabolism are not equally impaired. As hepatic dysfunction progresses in cirrhotic patients, reduced synthesis of albumin occurs that leads to a decrease in plasma protein binding of drugs. For drugs that are more than 90% protein-bound this increase in the free drug fraction may be substantial and have serious clinical consequences.

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3 It is imperative that a liver cirrhosis score such as the Child-Pugh Classification system (Table 1)
4 be obtained before therapy and monitored frequently thereafter. The synthetic function may be so
5 significantly impaired in a patient with a Child's-Pugh C score, that for safety reasons they
6 should not be treated.
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11 These issues highlight the difficulties surrounding the use of systemic therapies in HCC and
12 partly explain the disappointing results obtained with cytotoxic agents. Clearly there is a need for
13 effective novel systemic therapies if an impact is to be made in the treatment of advanced HCC.
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Novel Therapeutic Targets for the Treatment of HCC

HCC is notable for its highly aggressive behaviour, hypervascularity, portal and hepatic vein invasion, and early metastasis. Angiogenic factors such as vascular endothelial growth factor (VEGF), platelet-derived endothelial growth factor, and basic fibroblast growth factor released from the tumour itself, inflammatory cells and/or tumour stromal cells participate in the neovascularisation of HCC [26-28]. Aberrant VEGF expression is a prominent clinical feature in HCC and may correlate with HCC tumour invasion and metastasis [29] and may contribute to the development of the stroma in HCC [30].

The hypervascular nature of HCC has led to the exploration of antiangiogenic agents as a treatment for advanced HCC. The first of these agents investigated was thalidomide, but poor tolerability limited treatment and no clinical benefit was demonstrated [31]. Median progression free survival was 2.1 months and median overall survival was 5.5 months consistent with limited efficiency. Toxicity was significant with fatigue and severe fatigue reported in 75% and 20% of patients respectively.

High levels of VEGF have been associated with inferior survival in HCC [32, 33] and as a consequence bevacizumab, a humanised monoclonal antibody against VEGF has been investigated in the treatment of advanced HCC. In addition to its potential direct antiangiogenic effects, bevacizumab may enhance chemotherapy administration by “normalising” tumour vasculature and decreasing elevated interstitial pressure in tumours [34, 35]. Bevacizumab has been investigated in a phase II study in combination with GEMOX [36]. The objective RR was 20% and 27% had stable disease. The median OS was 9.6 months and median progression free survival (PFS) was 5.3 months, with the 3 and 6 month PFS approaching 70% and 48% respectively. The regimen could be safely administered with close monitoring in the majority of patients.

The epidermal growth factor receptor/ human epidermal growth factor receptor 1 (EGFR/HER1) and its ligands EGF and transforming growth factor- alpha (TGF- α) are important in cell proliferation, as well as motility, adhesion, invasion, survival and angiogenesis [37, 38]. It has been suggested that hypomethylation of the EGF receptor gene may be associated with the development of HCC [39]. Studies have indicated that EGFR/HER1 is actively expressed in

human hepatoma cells and that EGF may be one of the mitogens needed for the growth of hepatoma cell lines [40]. Erlotinib is an orally active, potent, selective inhibitor of the EGFR/HER1-related tyrosine kinase enzyme. It inhibits EGF-dependent proliferation of cancer cells and blocks cell-cycle progression into the G1 phase. Its use in advanced HCC was investigated in a phase II study of thirty eight patients, 47% of whom had received prior chemotherapy [41]. 32% were progression free at six months, and three patients had partial radiologic responses of 2, 10 and 11 months duration. Disease control was seen in 59% and median overall survival time was 13 months. Toxicities were predominantly cutaneous and 24% of patients required dose reductions because of toxicity. Toxicities were greater in those with Child-Pugh classification B who were more likely to experience grade 3 or 4 toxicity than those with Child-Pugh A classification again highlighting the need for careful stratification of patients.

A phase II trial of bevacizumab and erlotinib in advanced HCC has recently been reported by Thomas *et al* [42]. 62.5% were progression free at 16 weeks which was the primary endpoint. Ten patients achieved a partial response with an overall RR (intent to treat) of 25%. Median PFS was 39 weeks and median OS was 68 weeks. Gastrointestinal haemorrhage occurred in 12.5% of patients, one episode of which was fatal. Clearly haemorrhage is a concern in patients with cirrhosis who may have portal hypertension, varices or coagulopathy. This activity however is felt to be clinically meaningful to warrant further evaluation in randomised trials.

The Development of Sorafenib in HCC

Recently interest has focussed on the ubiquitous Raf-mitogen-activated protein kinase/extracellular signal-related kinase (MEK)-extracellular signal-related kinase (ERK) signalling pathway (Raf/MEK/ERK). This has a major role in the regulation of cell proliferation, survival and differentiation [43]. Dysregulated signalling via Raf is associated with the development of solid tumours [43, 44]. The MAPK pathway includes a cascade of phosphorylation events involving at least four well characterised kinases; ras, raf, mitogen-activated protein (MAP) extracellular kinase, and extracellular signal-regulated kinases (ERK). N-ras mutations are found in HCC, haematological malignancies and melanoma [45], whereas K-ras mutations are found in pancreatic cancer, non-small-cell lung cancer [45] and colorectal cancer (CRC) [46]. Overactivation of receptor tyrosine kinases (RTKs) such as vascular endothelial growth factor receptor (VEGFR)-2/-3, platelet-derived growth factor receptor

(PDGFR)- β , and epidermal growth factor receptor (EGFR), as a result of either activating mutations or overexpression of their growth factor ligands, can result in aberrant signalling through Raf, dysregulated cell growth, and cancer [43, 44, 47].

Both angiogenesis and signalling through the Raf/MEK/ ERK cascade play critical roles in the development of HCC. Several authors have described an increase in the expression and activity of these signalling intermediates in the MAPK pathway in HCC cell lines, in *in vivo* models, and human tumour specimens[48-52]. Furthermore, treatment of HCC cells with a MEK inhibitor reduces cell proliferation and induces apoptosis [53]. Therefore, inhibition of angiogenesis and Raf/MEK/ERK signalling may represent an attractive approach for the treatment of HCC.

Sorafenib is an oral multikinase inhibitor that has shown efficacy against a wide variety of tumours in preclinical models[54]. It has been shown to block tumour cell proliferation and angiogenesis by inhibiting serine/threonine kinases (c-RAF, and mutant and wild type BRAF) as well as the receptor tyrosine kinases VEGFR2 and VEGFR3, PDGFR, FLT3, Ret, and c-KIT [54, 55]. It has also been reported that sorafenib induces apoptosis in human leukaemia cells[56] and other human tumour cell lines [57] through the inhibition of the translation down-regulation of myeloid cell leukaemia-1 (Mcl-1), a Bcl-2 family member. Inhibition of eIF4E by sorafenib in leukaemia cells appears to be independent of the activity on the MEK/ERK pathway [56], suggesting a possible linkage between eIF4E and translational control of Mcl-1.

Recent findings have demonstrated that the antitumour activity of sorafenib in HCC models may be attributed to inhibition of tumour angiogenesis (VEGFR and PDGFR) and direct effects on tumour cell proliferation/survival (Raf kinase signalling dependent and signalling-independent mechanisms) [58].

Aberrant activation of the Raf/MEK/ERK signalling pathway has been associated with RCC and HCC tumours [48, 59], in addition to there being an overexpression of angiogenic growth factors such as VEGF, and their receptors which signal through Raf. There is therefore a solid scientific rationale for investigating the use of Sorafenib in these tumour types as it blocks tumour cell proliferation by targeting the Raf/MEK/ERK signalling at the level of Raf kinase, and exerts an antiangiogenic effect by targeting VEGF-2/-3, and PDGFR- β tyrosine kinases [54].

Sorafenib has been investigated as monotherapy in four phase I trials in patients with advanced refractory solid tumours [60-63] and demonstrated preliminary activity in tumour types including renal cell carcinoma (RCC), HCC and CRC. Sorafenib was mostly associated with durable disease stabilisation, while two patients (one each with RCC and HCC) had partial responses [60]. Prolonged (> 6 months) disease stabilisation was reported in a total of eight patients (18%) including four with CRC and two with HCC who were treated continuously with sorafenib [60]. In addition five of these patients (11%) had stable disease for > 1 year.

Results from the four phase I trials show that most patients experienced drug related adverse events, including fatigue, diarrhoea, and skin toxicities. These were mainly mild to moderate and manageable by dose reduction or cessation of treatment. Dose limiting toxicities such as skin toxicities, diarrhoea and fatigue predominantly occurred at the higher doses (600 and 800mg twice daily) across the four trials, but were relatively infrequent at lower doses the maximum tolerated dose (MTD) was determined to be 400mg twice daily. At the MTD of 400mg twice daily, the continuous dosing schedule was not associated with dose limiting toxicities or significant grade 3 or 4 toxicities [60].

Phase II studies have confirmed that a continuous 400mg twice daily dosing schedule has disease stabilising effects in patients with advanced refractory RCC and HCC [64, 65]. Furthermore results from the phase III TARGETs trial have shown that Sorafenib at 400mg twice daily, significantly prolonged progression-free survival versus placebo in patients with advanced, treatment- refractory RCC (5.5 months versus 2.8 months $p < 0.01$) and with an acceptable risk-benefit ratio for toxicities [66].

Results of Phase II and III trials of Sorafenib in advanced HCC.

A phase II trial of sorafenib in advanced HCC was prompted on the background of the a confirmed partial response in a phase I trial as detailed above [60] and a strong scientific rationale for its rationale based on the importance of VEGF and Raf/MEK/KRK signalling in HCC.

This was a multicentre, international phase II trial [65] in previously untreated patients with Child-Pugh A or B inoperable HCC and ECOG performance status (PS) of 0 or 1. Patients received sorafenib 400mg twice daily continuously until disease progression or unacceptable drug-related toxicities occurred. Up to two dose reductions and a recovery time of up to 3 weeks were allowed for drug related toxicities prior to the need for treatment cessation.

Of 137 patients treated, 3 patients (2.2%) achieved a partial response and 46 (33.6%) had stable disease for at least 16 weeks. Median time to progression was 4.2 months and median overall survival was 9.2 months. These results compare favourably with single agent and combination chemotherapy regimens [19] and with a more favourable toxicity profile. The most common drug-related adverse events were dermatological, constitutional and gastrointestinal symptoms.

Relatively infrequent dose-limiting toxicities were observed with no grade 4 toxicities and grade 3 toxicities of fatigue (9.5%), diarrhoea (8.0%) and hand-foot syndrome (5.1%). Sorafenib was equally well tolerated between Child-Pugh A and B patients.

Several biomarkers have been shown to have potential predictive significance in HCC [67, 68]. Because the Raf/MEK/ERK pathway has a significant role in HCC and is targeted by sorafenib, it has been proposed that the active form of ERK, phosphorylated ERK (pERK) may be a useful biomarker. This hypothesis was explored by Abou-Alfa *et al* and analysed tissue for tumour-cell pERK in 33 patients [65]. Staining was most intense in nuclei of tumour cells consistent with translocalisation of pERK to the nucleus after activation [69]. Furthermore, HCC patients whose tumours expressed higher baseline pERK levels had a longer TTP following treatment with Sorafenib suggesting that higher levels of pERK may correlate with sensitivity or responsiveness to Sorafenib.

White blood cells (WBCs) and peripheral blood mononuclear cells (PBMNCs) as the main source of RNA isolated from whole blood, are considered a “surrogate tissue” relative to a primary tumour or metastasis [67]. Therefore gene- expression patterns of WBCs and PBMNCs can be a molecular signature of a tumour that provides information on histological stage or potential to respond to treatment. RNA expression data from Abou-Alfa *et al* whilst encouraging was not sufficient to distinguish a panel of genes that distinguished nonprogressors from

progressors. Cell-based and genomic analyses would undoubtedly advance the discovery of new biomarkers and help refine treatment criteria and patient selection.

A large, multicentred, randomised, placebo-controlled phase III trial was conducted by Llovet *et al* to evaluate the safety and efficacy of sorafenib versus placebo in patients with advanced unresectable HCC not amenable to locoregional therapy [70]. Patients were required to have advanced measurable HCC and no prior systemic therapy, Child-Pugh classification A and ECOG PS 0-2. Six hundred and two patients were randomised to either sorafenib 400mg twice daily or placebo.

Based on 321 deaths (143 in Sorafenib treated patients and 178 in the placebo group), the hazard ratio (HR) for overall survival (OS) of sorafenib versus placebo treated patients was 0.69 (96% CI: 0.55, 0.87; $p=0.0006$). This represented a 44% improvement in OS for sorafenib versus placebo which met early stopping criteria. Median OS was 10.7 months for the sorafenib group versus 7.9 months in the placebo group. The second primary end point of the study, time to symptomatic progression demonstrated no statistically significant difference. This in may in part be due to the absence of an appropriate tool for measuring quality of life in this population as the median time to progression was longer in the Sorafenib group (5.5 versus 2.8 months $p=0.000007$).

The incidence of serious adverse events was similar in both groups (52% versus 54% for sorafenib versus placebo. The most frequent grade 3/4 events were diarrhea (11% versus 2%), hand- foot syndrome (8% versus 1%), fatigue (10% versus 15%) and bleeding (6% versus 9%) for sorafenib versus placebo.

At the European Cancer Conference in September 2007 results of a randomized phase II study comparing placebo and doxorubicin with sorafenib and doxorubicin in 96 patients with advanced HCC were reported [71]. As with the sorafenib monotherapy trial the trial was unblinded on the recommendation of the Data Safety Monitoring Board. The analysis demonstrated highly significant improvements in time to progression (2.8 months versus 8.5 months) and overall survival (5.6 months v 14.0 months).

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Conclusions and Future Directions

Given the lack of benefit derived from cytotoxic chemotherapy regimens in the treatment of advanced HCC, future hope seems directed towards the novel targeted agents. Research continues to investigate the key mechanisms of hepatocarcinogenesis and identify key molecular targets for potential therapeutic interventions. The heterogeneity and the underlying medical problems associated with this disease safety and toxicity profiles are of paramount importance when assessing the benefits of a novel therapeutic agent. Whilst establishing the effectiveness of the newer molecularly targeted therapies it is important to establish the relevance of disease stabilization and progression free survival as potential end points given the cytostatic rather than cytotoxic mode of activity. In addition the identification of potential surrogate markers for disease response may help to more effectively establish those who may derive benefit from newer therapies.

Two recently reported trials have demonstrated significant improvements in survival with sorafenib both as a monotherapy[70] and in combination with doxorubicin compared to control groups [71]. This establishes sorafenib as a new standard of care for patients with advanced HCC not amenable to locoregional therapy. Further research may elucidate the optimal schedule of administration. In addition, its role as an adjuvant therapy following both surgery and chemoembolisation require investigating.

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Table 1. The Child-Pugh Classification system.

Variable	Score 1	Score 2	Score 3
Bilirubin (mg/dl)	<2.0	2-3	>3.0
Albumin (g/l)	>3.5	3.5-2.8	<2.8
PT (INR)	<1.7	1.7-2.3	>2.3
Ascites	Absent	Mild to moderate	Severe/refractory
Encephalopathy	Absent	Mild	Severe

Class A: 5-6 points, Class B: 7-9 points, Class C: 10-15 points.

Abbreviations: INR, International Normalised Ratio; PT; Prothrombin time.

Adapted from Schwartz et al [72].