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Future Trends in the Management of Advanced Hepatocellular Carcinoma (HCC)

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1. Introduction

Liver Cancer is the 6th most common cancer worldwide. It is the 3rd most common cause of cancer-related death and accounts for 85% to 90% of primary liver cancers. It is 2.4 times more common in men than women. The worldwide incidence of the disease is 626,162 per year and the worldwide mortality 598,321 persons per year, making HCC the most common cause of cancer related death in the world. (Parkin et al., 2005)

Most patients with HCC also suffer from coexisting cirrhosis, which is the major clinical risk factor for hepatic cancer and is correlated to hepatitis B virus or hepatitis C virus (HCV) infection. However, cirrhosis from non-viral causes such as alcoholism, hemochromatosis and primary biliary cirrhosis are also associated with an elevated risk of HCC. Furthermore, concomitant risk factors such as

HCV infection in addition to alcoholism, tobacco use, diabetes or obesity increase the relative risk of HCC development, as numerous studies in humans and animal models have shown. The incidence of HCC varies by geographic area worldwide. Research has shown that Southeast Asia and sub-Saharan Africa have an incidence rate of HCC that ranges from 150 to 500 per 100 000 population, primarily because of the endemic nature of hepatitis B and C in those regions.

Patients at the early stage are those who present with an asymptomatic single HCC with the nodule < 5 cm in diameter or ≤ 3 in number. Patients exceeding these limits, but free of cancer-related symptoms and vascular invasion or extrahepatic spread, are considered at the intermediate stage. The patients with the cancer-related symptoms and vascular invasion or extrahepatic spread are deemed at the advanced stage. HCC is frequently diagnosed at the late stage and has a high mortality rate. Surgical resection is a potentially curative therapy for HCC, however, only a minority of HCC patients are eligible for curative hepatectomy. Comprehensive therapy for HCC has become the focus of interest in recent years.

In HCC patients the prediction of prognosis is more complex than in patients with other solid tumors because the underlying liver function also affects prognosis.

Several staging systems that separate patients into prognostic groups and serve to select appropriate treatment have been developed. Historically, HCC was classified by tumor,

node, metastasis (TNM) staging or the Okuda classification, but they do not distinguish between early and advanced stages. In the recent years 5 new classifications have been developed (Table 1):

- Japan Integrated Staging (JIS)
- Group d'Etude de Traitement du Carcinoma Hepatocellulaire (GRETCH)
- Cancer of the Liver Italian Program (CLIP)
- Barcelona Clinic Liver Cancer staging (BCLC)
- Chinese University Prognostic Index (CUPI)

but none of these staging systems has received universal acceptance.

Parameter	Okuda	CLIP	CUPI	TNM6	JIS	GRETCH	BCLC
Cirrhosis-related parameters							
Albumin	X	X			X		X
Bilirubin	X	X	X		X	X	X
Ascites	X	X	X		X		X
PT/INR		X			X		X
Encephalopathy		X			X		X
Alkaline phosphatase			X			X	
Tumor-related parameters							
Tumor stage/ disease extent	X	X	X	X	X		X
Portal vein thrombosis		X				X	X
Alpha fetoprotein		X	X			X	
Asymptomatic			X				
Performance status						X	X

INR = international normalized ratio; PT = prothrombin time;
TNM-6 = tumor, node, metastasis classification, 6th ed.

Table 1. Comparison of Staging Systems for HCC

The BCLC staging system was first introduced at 1999 and constitutes an evolving approach as it has regularly incorporated changes that have emerged since its first publication. (Llovet et al., 1999) On the other hand, links five stages of the disease with the appropriate therapeutic options and has been endorsed by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of Liver (EASL) (Forner et al., 2010).

2. The current management

Historically, the diagnosis of HCC was almost always made when the disease was in advanced stage and when patients were symptomatic and presented with a variable degree

of liver function impairment. At this stage, no treatment had any chance to be effective or to significantly improve survival rates. Additionally, the morbidity associated with therapeutic options was extremely high.

Today, many patients are diagnosed at an early stage when liver function is well preserved and there are no cancer related symptoms. On the other hand, there are several active treatment modalities available that will potentially improve survival.

2.1 Surgical treatment options for very early-stage HCC

The only curative approach for HCC is surgery (resection or transplantation). Surgical treatments are applicable in 10% to 15% of patients with HCC at first diagnosis, and only in 2% to 5% of those with recurrent HCC.

Although, surgical resection is the treatment of choice for HCC non cirrhotic patients, these people account only 5% of the HCC cases in Western countries and almost 40% in Asia. These patients will tolerate major resections with low morbidity. On the other hand, cirrhotic candidates for resection must to be carefully selected because of the high risk of postoperative liver failure and the increased risk of death.

Surgical resection historical 5-year survival rate is 30% to 40% and the 5-year progression free survival (PFS) rate as high as 48%, but the vast majority of these patients develop recurrence or secondary primary tumors. For patients who undergo resection, recurrence rates can be as high as 50% at 2 years. (Liu et al., 2004)

Liver transplantation is now part of the conventional armamentarium for the treatment of HCC.

Although survival rate was improved to 61.1% from 1996-2001 and the 5-year overall survival (OS) rates of 58% to 74%, the morbidity and death rates in the early and intermediate follow up period are higher than in resection surgery in optimal candidates. (Mazzaferro et al., 2009)

But unfortunately, the vast majority of HCC patients present with advanced or unresectable disease. No surgical treatments are applicable in 70% to 85% of patients with HCC at first diagnosis and in 50% to 70% of those with recurrent HCC. The 3-year survival rate for these patients is 10% to 40% . (Bruix J& Sherman, 2011)

2.2 Local ablative therapy for early-stage HCC

The two most widely used local ablative techniques are radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI) and are used in small (< 3 cm) solitary tumors.

RFA induces temperature changes by using a high-frequency alternating current applied via electrodes placed within the tissue to generate areas of coagulative necrosis and tissue desiccation. During RFA treatment, heat energy generated by high-frequency alternating currents targeted at the living tissues causes protein denaturation at a temperature of 60-110℃ through ionic vibration, resulting in coagulative necrosis of the target lesion. In addition, RFA treatment stimulates the immune system and provides an easy way to achieve in vivo vaccination against tumoral antigens. RFA can be performed intraoperatively or under image guidance.

Intraoperatively RFA is generally indicated for HCC patients who are not candidates for either liver resection or transplantation. HCC patients are required to have ≤ 5 nodules, each < 3 cm in diameter, no evidence of vascular invasion or extrahepatic spread, 0 score performance status of the Eastern Cooperative Oncology Group (ECOG), and liver cirrhosis in Child-Pugh class A or B. The more versatile radiofrequency probes allow ablation of nodule > 5 cm. When complete resection by major hepatectomy is dangerous because of difficult nodule location, selective use of intraoperative RFA will be helpful. The integration of intraoperative RFA into resection surgery contributes to complete removal of nodules with adequate margin, diminishes the extent of parenchymal resection, and improves the resectability rate for patients with advanced HCC.

Ultrasound or CT guided (percutaneous) RFA is now the first choice treatment to inoperable HCC.

Depending on the type of electrode used, ablation diameters up to between 5 and 7 cm are now possible.

PEI involves a needle being inserted into a liver tumor and absolute or 95% ethanol slowly injected into the lesion to induce nonselective protein degradation and cellular dehydration leading to necrosis. RFA has been shown to be superior to PEI in tumor response and long-term survival.

Response rate for RFA is 91% vs 82% for PEI and the 1- and 2-year local recurrence-free survival rates are 98% and 96% for RFA vs 83% and 62% for PEI. The 4-year survival rate is 74% vs 57%. RFA present a 46% lower risk of death, a 43% lower risk of overall occurrence, and an 88% lower risk of local tumor progression than PEI.

Other techniques such as laser, microwave, high intensity ultrasound, cryotherapy or acetic acid injection are less common or validated in terms of efficacy and safety.

2.3 Regional therapy for intermediate-stage HCC: Transarterial chemoembolization (TACE)

The portal vein supplies 75% to 85% of the blood to the liver, while the hepatic artery provides 20% to 25%. In HCC, the hepatic artery supplies 90% to 100%.

Enough evidence exists on the effectiveness of conventional TACE in prolonging survival in intermediate HCC patients with well preserved liver function (Child-Pugh A class). (El-Serag et al., 2008).

Candidates for TACE should not have advanced HCC, should be no major portal vein invasion, and liver function should be preserved.

Embolization agents (generally gelatin or microspheres) are administered with a high-viscosity mixture of lipiodol and chemotherapy (doxorubicin, mitomycin, or cisplatin), blocking blood flow to the tumor.

At 1 and 2 years, the survival probabilities are 82% and 63% for chemoembolization with doxorubicin or cisplatin versus 63% and 27% for supportive care (P =0.009). Is reported 3-year survival rates of 26% vs 3% for supportive care.

A meta-analysis has shown a beneficial effect on 2-year survival (odds ratio = 0.53, P = 0.017) and a median survival of 20 vs 16 months for conventional therapies.

There is no good evidence for the best chemotherapy agent and the optimum treatment strategy.

The improved survival rates with TACE have led to its use as a bridge therapy to liver transplantation or resection. TACE may increase the chance of a patient staying on the transplant list and acquiring an organ, as well as decrease recurrence and prolong survival.

TACE was investigated in combination with RFA and was compared with TACE alone and showed increased 1-year survival (100% vs 67%, P = 0.04) and mean survival (25.3 mo ± 15.9 vs 11.4 mo ± 7.3, P < 0.05).

TACE combined with RFA in HCC patients after hepatectomy was compared with single TACE or RFA treatment. The intrahepatic recurrence rate was lower in the combination group vs TACE (20.7% vs 57.1%, P = 0.002) and vs RFA (20.7% vs 43.2%, P = 0.036). The overall 1-, 3-, and 5-year survival rates were 88.5%, 64.6%, and 44.3% for the combination, 65.8%, 38.9%, and 19.5% for TACE, and 73.9%, 51.1%, and 28.0% for RFA.

Neoadjuvant and adjuvant TACE have shown little effect (Raul at al., 2011).

2.4 Systemic therapy for advanced-stage HCC

No significant survival advantage has been demonstrated with systemic chemotherapy. Most published studies report response rates of 0% to 25%. Of the single agents, doxorubicin is perhaps most widely used. Gemcitabine plus Oxaliplatine (GEMOX) appears to be more active than gemcitabine alone (Table 2). Tamoxifen showed no antitumoral effect or survival benefit. The presence of estrogen receptors in advanced HCC was the rationale for antiestrogen treatment.

Agent	Year	2008	Pts	Response Rate, %	Median Survival, mo
Doxorubicin	2005	III	94	11	6.8
PIAF	2005	III	94	21	8.7
Nolatrexed	2007	III	222	1	5.6
Paclitaxel	1998	II	20	0	3.0
Capecitabine	2000	II	37	13	6.0
Irinotecan	2001	II	14	7	8.2
Gemcitabine	2002	II	30	0	6.9
GEMOX	2007	II	34	18	11.5
XELOX	2007	II	50	6	9.3
Capecitabine/cisplatin	2008	Cohort *	178	20	10.5

* Retrospective analysis.
PIAF = cisplatin, interferon, doxorubicin, 5-fluorouracil; GEMOX = gemcitabine and oxaliplatin; XELOX = capecitabine (Xeloda), oxaliplatin.

Table 2. Summary of Responses to Systemic Chemotherapy in HCC

2.5 Sorafenib (Nexavar)

Sorafenib (Nexavar) is a multikinase inhibitor (RAF-tyrosine kinase/VEGF/c-KIT/PDGFR-β inhibitor) and is a new treatment approach for HCC.

Is an oral VEGF- PDGF inhibitor with activity against RAF/MEK/ERK pathway that block both tumor cell proliferation and angiogenesis.

Preclinical studies reported antitumor activity in HCC cells and xenograft models.

Results of a phase II study involving patients with advanced HCC and Child-Pugh class A and B cirrhosis with a dose of 400 mg twice daily induced a PR in 2.2% of patients, a minor response in 5.8%, and stable disease lasting 16 weeks in 34%. Median time to progression (TTP) was 4.2 months, and median OS was 9.2 months.

The SHARP study, a randomized placebo controlled phase III trial, showed improved overall survival for the Sorafenib group (44% vs 33% for the placebo group). Median survival (MS) was 10.7 months vs 7.9 months. Drug related adverse events were more frequent in the Sorafenib group than in the placebo group (80% vs 52%) and included diarrhea, weight loss, hand-foot skin reaction, anorexia, alopecia, and voice changes. The majority of these were grade 1 or 2 in severity. (Llovet et al., 2008). A similar design phase III Asian Pasific study revealed a survival benefit of similar magnitude, mostly for patients with hepatitis B virus infection, but the median overall survival was significantly lower (6.5 months for the Sorafenib group vs 4.2 for the placebo group). (Liu et al., 2009).

Thus, Nexavar is approved from 2007 in U.S.A. and E.U. for the treatment of advanced HCC in Child-Pugh A cirrhotic patients.

The results of SHARP trial was a milestone in the treatment of HCC and stimulated the search for similar compounds targeting other molecular alterations, in particular because combination treatments are postulated to be a promising approach through synergistic anti-tumoral effects (Rimassa & Santoro, 2010)

3.The future trends

3.1 Sorafenib in cirrhosis stage B and C

Recently published papers report data of patients with HCC in different stages of liver cirrhosis treated with Sorafenib. Small benefit and only for patients without extrahepatic metastatic disease was observed.

3.2 Sorafenib as adjuvant treatment

An important goal of HCC research and therapy is the prevention of tumor recurrence in patients previously treated with resection or local ablation, since 70% of this population will develop HCC recurrence within 5 years. Recurrence could result from intrahepatic metastases that remain after incomplete treatment of primary tumor or through formation of new tumors, caused by the persistence of the carcinogenic field present in the cirrhotic liver. The molecular features of each recurrent tumor type are likely to differ. Sorafenib is tested now an adjuvant treatment in the STORM trial.

3.3 Sorafenib in several combinations

The efficacy of Sorafenib in patients with advanced HCC was also tested in combination with several chemotherapeutic agents. At the moment there are 65 registered trials testing Sorafenib (alone or in combination with other agents), in phases I-IV.

3.3.1 Sorafenib + doxorubicin vs placebo + doxorubicin (phase II study)

Although a higher response rate and acceptable safety profile have been reported from several small studies, the combination of this drugs is not yet been approved for the treatment of advanced HCC.

Patients with Eastern Cooperative Oncology Group performance status of 0–2, Child-Pugh A cirrhosis, and no prior systemic therapy received Doxorubicin at 60 mg/m^2 intravenously every 21 days (cycle) plus either Sorafenib at 400 mg orally twice daily or placebo, for a maximum of six cycles of Doxorubicin. Patients could continue with single-agent Sorafenib or placebo afterward. The primary end point was TTP by independent review. The median OS and TTP were 13.7 and 8.6 months for the Doxorubicin plus Sorafenib arm and 6.5 and 4.8 months for the Doxorubicin plus Placebo arm, respectively. The response rate was 4% in the Doxorubicin plus Sorafenib arm and 2% for the Doxorubicin plus Placebo arm. The safety profiles seemed to be comparable for both groups, including grade 3-4 neutropenia in almost 50% of patients . (Abou-Alfa et al., 2010).

3.3.2 Sorafenib + erlotinib vs sorafenib + placebo (as first line treatment)

Erlotinib is an orally administered inhibitor of tyrocine kinase activity of the epidermal growth factor receptor (EGFR). Results from two small, Erlotinib monotherapy studies, in patients with advanced HCC have been reported overall survival rates ranging between 6.25 and 13 month and time to tumor progression rates raging between 6.5 and 3.2 months. At the moment, a randomized, double-blind, phase III study comparing Sorafenib with the combination of Sorafenib and Erlotinib is ongoing.

Furthermore, ongoing and planed clinical studies will evaluate the benefit of combining molecular-targeted therapies that block complementary pathways that are activated in HCC (Villanueva & Llovet, 2011).

3.3.3 Sorafenib in real-life setting studies

In addition to randomized controlled trials (RCTs,) because the treatment of HCC is complex and confounded by comorbidities, studies evaluating therapy in the real-life setting are also essential to allow physicians to make fully informed treatment decisions. Among these is the Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON) study. This is an international, prospective, open-label, multicenter, noninterventional study of patients with unresectable HCC for whom the decision has been taken to treat with sorafenib. The aim of the GIDEON study is to compile a large robust database of information from sorafenib treated patients that can be analyzed to gain a detailed understanding of the local, regional, and global factors influencing the management of patients with HCC. As such, detailed medical information

from 3000 patients globally over 5 years will be obtained, and information regarding the practice patterns of the treating physicians will also be collected, making it potentially the largest study of its kind in this patient population. The primary objective of this study is to evaluate the safety of sorafenib in the real-life clinical setting. Secondary objectives include: efficacy evaluations (OS, progression-free survival, time to progression, response rate, and rate of stable disease); duration of therapy; regional and global methods of patient evaluation, diagnosis, and follow-up; evaluation of comorbidities and their influence on treatment and outcome; and evaluation of regional and global practice patterns of the physicians involved in the care of these patients.

On the other hand, given the known antiangiogenic properties of sorafenib, the combination of TACE with sorafenib holds promise and clinical trials investigating this therapeutic approach are ongoing (Sorafenib or Placebo in Combination with Transarterial Chemoembolization for Intermediate-stage HCC [SPACE] trial. Indeed, given that DEB (Drug-Eluting Bead) -TACE has shown better tolerability than TACE, the combination of sorafenib with DEB-TACE is also promising.

3.4 Antiangiogenic agents

HCC is a hypervascular tumor with overexpression of several proangiogenic factors such as vascular endothelial growth factor (VEGF). On the other hand, high microvessel density have been observed in HCC tissue samples. Because of VEGF expression levels are directly associated with low survival rates, the inhibition of angiogenesis can represent a potential target in HCC and several antiangiogenic agents have entered clinical studies.

3.4.1 Sunitinib

Is an oral multikinase inhibitor, approved for the treatment of GIST after progression or intolerance to imatinib mesylate and also for the treatment of advanced or metastatic kidney cancer, that targets receptors of tirosine kinases including VEGFR-1 and -2, PDGFRalpha/beta, c-KIT, FLT3, and RET kinases.

Sunitinib has been shown to possess antitumoral activity and an acceptable safety profile in several Phase II trials in patients with advanced HCC. But, a higher toxicity and a greater number of side effects were observed in HCC patients than in patients with other neoplasias. For this reason, the drug usually was administered in a lower dose in HCC trials (37.5mg vs 50 mg).

In a phase II European/Asian study on 37 patients, the original starting dose was 50 mg/d for 4 consecutive weeks followed by two rest periods. The primary end point was the evaluation of the overall response rate according to Response Evaluation Criteria in Solid Tumours criteria. The main grade grade 3 and 4 toxicities observed were thrombocytopenia (43%), neutropenia (24%), neurological symptoms (24%), fatigue (22%) and hemorrhages (14%). Forty-three percent of patients required a dose reduction and 4 patients died due to the treatment. Median TTP was 5.3 months and OS was 9.3 months. (Faivre et al., 2009).

Another phase II study evaluated the efficacy and tolerability of sunitinib at the initial dose of 37.5 mg/d for 4 consecutive weeks followed by two rest periods in 34 patients with advanced HCC. Grade 3 and 4 toxicities observed were neutropenia (12%),

thrombocytopenia (12%), fatigue (12%), rash (6%), hand-foot syndrome (6%), hyperbilirubinemia (6%) and hypertension (6%). One patient died of liver failure due to a rapid disease progression. Stable disease was highlighted in 47% of patients for at least 12 weeks. Progression free survival was 4 months and the median overall survival of 9.9 months. (Zhu et al., 2009).

Thus, the efficacy and tolerability of the drug were tested recently in a phase III trial, but the study was stopped prematurely because of lack of efficacy and significant adverse events (Table 3).

Dose schedule and sample size	37.5 mg 4 weeks on/2 weeks off (n = 34)	50 mg 4 weeks on/2 weeks off (n = 37)	37.5 mg 4 weeks on/2 weeks off (n = 17)	37.5 mg continuous (n = 45)
Objective response rate, n (%)	1 (2.9)	1 (2.7)	1 (5.9)	1 (2.2)
Disease control rate*	52%	38%	53%	42%
Overall survival (months)	9.8	8.0	-	9.3
Time to progression (months)	4.1	-	-	2.8
Progression-free survival (months)	3.9	3.7	-	2.8

Table 3. Phase II trials of SUNITINIB in advanced HCC

3.4.2 Brivanib

Is an oral dual inhibitor of VEGF and fibroblast growth factor (FGF) receptors signaling pathways, effective in mouse HCC xenograft models. A phace II study with Brivanid at the dose of 800 mg daily, as first and second line treatment in 96 patients with advanced HCC (unresectable locally advanced or metastatic disease) who did or did not receive pre-treatment, demonstrated a median TTP of 2.7 months (95% CI, 1.5-3.9), when the drug was administered as first line treatment and a median TTP of 1.4 months (95% CI, 1.4-2.6) when the drug was administered as second line treatment. Interestingly, a 50% decrease in serum AFP from baseline was seen in 40% of all patients. Additionally, reduction in collagen IV (a new serum angiogenesis biomarker) levels was observed to be associated with long term outcome. Most frequently observed grade 3-4 adverse events included fatigue (16%), high levels of AST (19%), hyponatremia (41%), hypertension (7.3%), diarrhoea (4.9%), and headache (4.9%). (Park et al., 2011).

Thus, Brivanib is now under evaluation in phase III studies in both the first-line setting in comparison with Sorafenib and in the Sorafenib-refractory setting in comparison with best supportive care in advanced HCC.

3.4.3 ABT-869

Is an orally active, potent and selective inhibitor of VEGF and platelet derived growth factor (PDGF) receptor families. ABT-869 showed potent antiproliferative and apoptotic properties in vitro and in animal cancer xenograft models using tumor cell lines that were "addicted" to signaling of kinases targeted by ABT-869. When given together with chemotherapy or mTOR inhibitors, ABT-869 showed at least additive therapeutic effects.

A Phase II study, when the drug was administered at 0.25 mg/kg daily in patients with Child-Pugh A cirrhosis reported response rate of 8.7% (95% CI, 1.1 - 28). For all patients (Child-Pugh A and B cirrhosis) median TTP was 112 days, median PFS was 112 days (95% CI, 61 - 168) and median OS was 295 days (95% CI, 182 - 333). The most common adverse events (AEs) were hypertension (41%), fatigue (47%), diarrhea (38%), rash (35%), proteinuria (24%), vomiting (24%), cough (24%) and oedema peripheral (24%). The most common grade 3/4 AEs were hypertension (20.6%) and fatigue (11.8%). Most adverse events were mild/moderate and reversible with interruption/dose reductions/or discontinuation of ABT-869. However, additional studies are required to determine the optimal dosing strategy especially in HCC patient population as frequent dose interruption or reduction was observed.

On the other hand, a phase III study comparing efficacy and tolerability of ABT-869 versus Sorafenib is ongoing.

3.4.4 Bevacizumab

Is a recombinant, humanized, monoclonal antibody against VEGF present direct anti-angiogenic activity and may enhance the efficacy of chemotherapy by normalizing the tumor vasculature and decreasing the elevated interstitial pressure in tumors. The drug has been studied both as monotherapy and in combination with cytotoxic and molecular targeted agents in patients with advanced HCC.

In a phase II study bevacuzimab was evaluated as monotherapy at two different dosages (5 mg/kg and 10 mg/kg) intravenously, once every 2 weeks, in patients with HCC with no overt extrahepatic metastases or invasion of major blood vessels. The median PFS was 6.9 months and the median OS was 12.4 months with 65% of patients progression-free at 6 months. (Siegel et al., 2008)

The drug was evaluated also in combination with chemotherapy (gemcitabine, oxaliplatine, capecitabine) in several phase II studies with response rates ranging between 11%-20% and median overall survival ranging between 9.6-10.7 months. (Zhu et al., 2006)

The combination of Bevacuzimab (10 mg/kg intravenously once every 14 days) with Erlotinib (150 mg orally daily) achieved a response rate of 25%, a median overall survival of 68 weeks and a median PFS of 39 weeks (Table 4).

Although the above studies demonstrated early evidence of antitumor activity of Bevacizumab in HCC and the reported tolerability profile was in general good, the increased risk of hypertension, thromboembolic events and bleeding requires further evaluation. On the other hand, because of the non-randomized trials and the small number of patients enrolled, the results must be confirmed in large randomized studies. The contribution, also, of chemotherapy and Erlotinib needs further investigation.

Study	Regimen	No. of patients	RR (%)	Median PFS/TTP (months)	Median survival (months)
Siegel et al.	B	46	13	6.9	12.4
Malka et al.	B	24	12.5	NR	NR
Zhu et al.	GEMOX-B	33	20	5.3	9.6
Sun et al.	CAPEOX-B	30	10	5.4	NR
Hsu et al.	Capecitabine-bevacizumab	25	16	4.1	10.7
Thomas et al.	B + Erlotinib	40	25	9.0	15.6

B: Bevacizumab only; CAPEOX-B: Capecitabine--oxaliplatin--bevacizumab; GEMOX-B: Gemcitabine--oxaliplatin--bevacizumab;
PFS: Progression-free survival;RR: Response rate; TTP: Time to progression.

Table 4. Phase II studies of bevacuzimab-based regimens in HCC

3.4.5 TSU-68

This agent is another oral multikinase inhibitor of VEGF receptor-2, PDGF receptor and fibroblast growth factor receptor, that was tested recently at a dose of 200 mg and 400 mg bid in patients with advanced HCC, in a phase I/II study. Safety and efficacy were evaluated. The median TTP was 2.1 months, and the median OS was 13.1 months. Common adverse events were hypoalbuminemia, diarrhea, anorexia, abdominal pain, malaise, oedema and AST/ALT elevation. The analysis of angiogenesis-related parameters suggests that serum-soluble vascular cell adhesion molecule-1 is a possible marker to show the response. (Kanai et al., 2011)

In another phase II study TSU-68 showed promising efficacy with a high safety profile, even in heavily pretreated (surgery, radiofrequency ablation, transcatheter arterial embolization, chemotherapy, or radiotherapy) HCC patients with Child-Pugh B liver cirrhosis. This study design with stepwise adjustment of doses based on liver function constitutes an appropriate approach for HCC. Additionally, a randomized phase II study of TSU-68 in patients with HCC treated by TACE showed a marginally but statistically significant efficacy to prolong PFS compared to TACE alone. The results suggests that the of TSU- 68 administration may improve the overall survival of patients treated by TACE.

3.4.6 Cediranib

CEDIRANIB is another potent oral inhibitor of vascular endothelial growth factor signalling with activity against platelet derived growth factor receptor beta (PDGFRb) and c-Kit. Also, is a potent inhibitor of both KDR (IC50\0.002 lM) and Flt-1 (IC50=0.005 lM) with activity against Flt-4 at nanomolar concentrations. The agent was evaluated in a phase II trial, but grade 3 toxicity (anorexia, hypertension and fatigue) was reported in the vast majority of patients. Thus, a new study was conducted at a dose of 45 mg once daily, for 28-day cycles, but with low efficacy rates. (Alberts et al., 2011)

A single-arm phase II study that uses AZD2171 at 30 mg daily to assess the tolerability and safety in advanced HCC is also ongoing.

3.4.7 Vatalanib or PTK787/ZK 222584 (PTK/ZK)

Vatalanib or PTK787/ZK 222584 (PTK/ZK) is an oral, anti-angiogenesis compound that blocks tyrosine kinase signaling from all known VEGF receptors (including VEGFR-1/flt-1, VEGFR-2/KDR, and VEGFR-3/ Flt-4, PDGFR, and the c-kit with a higher selectivity for VEGFR-2).

The compound was tested initially in an open-label, multi-center, phase I study to characterize the safety, tolerability, and pharmacokinetic profile. The agent was administered once daily at a dose of 750 mg to 1250 mg in patients with unresectable HCC. Patients were stratified into three groups with mild, moderate, and severe hepatic dysfunction, respectively, on the basis of total bilirubin and AST (aspartate aminotransferase)/alanine aminotransferase levels. The maximal tolerated dose was defined as 750 mg daily and 50% achieved stable disease.

Based on the results of this study, a phase 1-2 trial of PTK787/ZK222584 combined with intravenous doxorubicin was conducted. The results showed encouraging activity of the combination in treating advanced HCC patients and the commonest grade 3 or 4 nonhematological toxicities were mucositis (11%) and alopecia (7%). Grade 3 or 4 neutropenia was observed in 26% of patients and neutropenic sepsis in 7.2%.

3.4.8 Pazopanib (GW786034)

PAZOPANIB (GW786034) is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-Kit.

A Phase I study was conducted to determine the maximum tolerated dose, safety, pharmacokinetics, pharmacodynamics and efficacy of pazopanib in patients with locally unresectable and/or advanced HCC. Eligibility criteria included unresectable and/or metastatic HCC with at least one target lesion, recovery from prior systemic regimens, Eastern Cooperative Oncology Group performance status of 0 or 1, Child Pugh A, and adequate organ function. Doses of pazopanib were escalated from 200 mg once daily to 800 mg daily in a 3 + 3 design. In the 27 Asian patients enrolled, MTD was determined to be 600 mg once daily. The results showed a manageable safety profile in HCC at the maximum tolerated dose of 600mg QD. PR was observed in 7% of patients and stable disease of 4 months in 41% of patients. Median TTP at the maximum tolerated dose was 137.5 days (range, 4–280 days). Changes in tumour dynamic contrast-enhanced MRI parameters were seen following repeated dose pazopanib administration. (Yau et al., 2010)

3.4.9 NGR-hTNF

NGR-hTNF is a novel agent that selectively binds to aminopeptidase N (CD13), which is overexpressed in tumour blood vessels. In a phase II trial this agent was well-tolerated and the OS was 9.1 months. Of note, one complete response was observes in a Sorafenib-refractory patient and one partial response in a cirrhotic Child-Pugh B patient (Rimassa & Santoro 2010).

3.5 Epidermal Growth Factor Receptor (EGFR) inhibitors

The expression of several EGF family members, specifically EGF, TGF-a, heparinbinding epidermal growth factor, and EGFR, has been described in several HCC cell lines and tissues. Multiple strategies to target EGFR signaling pathways have been developed, and two classes of anti-EGFR agents have established clinical activity in cancer: monoclonal antibodies that competitively inhibit extracellular endogenous ligand binding, and small molecules that inhibit the intracellular tyrosine kinase domain.

3.5.1 EGFR tyrosine kinase inhibitors

ERLOTINIB: Two phase II clinical studies have evaluated the safety and efficacy of Erlotinib (Tarceva) provided at 150 mg daily in patients with advanced HCC. Partial response was observed in 9% and 0% of patients, and the median overall survival was 13 months and 25 weeks respectively, from the date of Erlotinib therapy initiation (Rossi et al., 2010).

GEFITINIB provided at 250 mg daily was examined in a single-arm phase II study (E1203) from the Eastern Cooperative Oncology Group. A two-stage design was used, and 31 patients were accrued to the first stage. The median PFS was 2.8 months (95% CI 1.5–3.9) and median OS was 6.5 months (95% CI, 4.4–8.9). The criterion for second stage accrual was not met, and the authors concluded that gefitinib as a single agent was not active in advanced HCC. 3.22% of patients had PR and 22.5% of patients presented stable disease, but the criterion for second stage accrual was not met and thus the study was stopped prematurely because of lack of efficacy.

LAPATINIB, a selective dual inhibitor of both EGFR and HER-2/NEU tyrosine kinases, also demonstrated modest activity in HCC. Among the 40 patients with advanced HCC, the response rate was 5%, the progression free survival 2.3 months, and OS of 6.2 months (Table 5).

3.5.2 Monoclonal antibodies against EGFR

CETUXIMAB is a chimeric monoclonal antibody against EGFR . In two phase II studies in patients with advanced HCC was administered at 400 mg/ m^2 intravenously, followed by weekly intravenous infusions at 250 mg/m^2. The reported median OS was 9.6 months, the median PFS 1.4 months and the median TTP 2 months.

The combination of cetuximab with gemcitabine and oxaliplatin (GEMOX) was evaluated in a phase II study. All patients received cetuximab at an initial dose of 400 mg/m2 followed by 250 mg/m2 weekly, gemcitabine 1000 mg/m2 on day 1, and oxaliplatin at 100 mg/m2 on day 2, repeated every 14 days until disease progression or limiting toxicity. The confirmed response rate was 20%, the disease stabilization rate 40%, the median PFS 4.7 months and the OS 9.5 months. The 1-year survival rate was 40%.

The combination of cetuximab with capecitabine and oxaliplatin was evaluated in a single-arm phase II study. Capecitabine was administered at 850 mg/m^2 twice daily for 14 days, oxaliplatin on day 1 at 130 mg/m^2 intravenously, and cetuximab at 400 mg/m^2 on day 1 followed by 250 mg/m^2 weekly in a 21-day cycle. Response rate was 10%, and TTP 4.3 months. The most common side effects were electrolyte abnormalities and diarrhoea (Table 5).

	Year	Pts.	RR (%)	Median PFS (months)	Median OS (months)
Erlotinib	2005	38	9	3.2	13
Erlotinib	2007	40	0	3.1	6.3
Lapatinib	2009	40	5	2.3	6.2
Lapatinib	2009	26	0	1.9	12.6
Cetuximab	2007	32	0	2	-
Cetuximab	2007	30	0	1.4	9.6
GEMOX + Cetuximab	2008	45	20	4.7	9.5
CAPEOX + Cetuximab	2008	25	10	4.3	-

CAPEOX: Capecitabine--oxaliplatin; GEMOX: Gemcitabine--oxaliplatin;
OS: Overall survival; PFS: Progression-free survival; RR: Response rate

Table 5. Phase II trials of EGFR inhibitors in HCC

3.6 Additional potential therapeutic targets

During hepatocarcinogenesis, multiple genetic and epigenetic changes occur, and different pathways are involved such as the PI3/Akt/mTOR, hepatocyte growth factor (HGF)/cMET, insuline-like groth factor (IGF) and its receptor (IGFR) pathways and finally the Wnt-β catenin pathway. Several agents targeting these pathways are in clinical development in advanced HCC.

3.6.1 mTOR Inhibitors (mammalian target of rapamycin)

During hepatocarcinogenesis, several genetic and epigenetic changes occur and multiple pathways are involved such as PI3K/Akt/mTOR. The mTOR is a key regulator of Growth Factor signaling pathways. Is an intracellular serine/threonine kinase in the PI3K/Akt signaling pathway.

mTOR activation promotes cell growth and proliferation, angiogenesis and cancer cell metabolism through increased nutrient uptake and utilization. Preclinical data have demonstrated that mTOR inhibitors were effective in inhibiting cell growth and tumour vascularity in HCC cell lines and HCC tumour models. The importance of the mTOR pathway in HCC was examined in a large comprehensive study with HCC and nontumoral tissues. Aberrant mTOR signalling (p-RPS6) was present in 50% of the cases and chromosomal gains in rapamycininsensitive companion of mTOR (RICTOR) in 25%. Positive p-RPS6 staining was found to correlated with HCC recurrence after resection.

SIROLIMUS (Rapamycin): Retrospective studies in patients who underwent liver transplantation for HCC have shown that patients who received sirolimus for immunosuppression had a much lower rate of tumour recurrence than those who received calcineurin inhibitors. In a pilot study Sirolimus was administered in patients advanced hepatocellular carcinoma. Overall, therapy with rapamycin was well tolerated. Most

common toxicities were thrombocytopaenia and anaemia. The observed median OS was 5.27 months and the median TTP was 3 months.

TEMSIROLIMUS: Temsirolimus is a soluble ester analogue of sirolimus. Temsirolimus has been approved by the FDA for treatment of advanced renal cell carcinoma and demonstrated a survival benefit as monotherapy by comparison with interferon alpha in a multicenter phase III trial. At the moment several studies with the drug as monotherapy or in combination (with Sorafenib or Bevacuzimab) are ongoing in patients with advanced HCC.

EVEROLIMUS (RAD001): This agent, an orally administered mTOR inhibitor, was evaluated initially in a phase I study. Totally 36 patients were treated at different dose levels on a daily or weekly schedule and data reported that the drug is moderately active in this setting. Dose-limiting toxicities observed included hyperbilirubinemia, high levels of alanine aminotransferase, thrombocytopenia, infection, diarrhea, and cardiac ischemia. On the other hand, reactivation of hepatitis B and C virus was observed in four and one patients, respectively. The disease control rate of 31 evaluable patients was 61% (10 of 16) and 46.7% (7 of 15, including one case of partial response) of patients receiving daily and weekly treatment, respectively.

In a phase I/II study everolimus was administered in 28 patients with advanced HCC and adequate hematologic, hepatic, and renal functions at 5 mg/day or 10 mg/day orally (6 weeks/cycle). The primary end points were determination of a safe dosage of everolimus (phase 1) and progression free survival at 24 weeks (phase 2). Grade 3-4 adverse events included lymphopenia , ALT and AST elevation, hyponatremia, anemia, hyperglycemia, proteinuria, rash, and hypoxia. One patient (4%) had partial response . The median progression free survival and overall survival were 3.8 months 8.4 months, respectively. The estimated progression free survival rate at 24 weeks was 28.6%.

Thus, a randomized phase III, double-blind, placebo-controlled, multicenter study to evaluate the efficacy of everolimus in adult patients with advanced hepatocellular carcinoma after failure of Sorafenib treatment (EVOLVE-1 Study) is ongoing (Tazi et al., 2011).

3.6.2 MEK inhibitors

HCC is characterized by frequent MEK/ERK activation in the absence of RAF or RAS mutation. A multicenter, single arm phase II study with a two-stage design was conducted with AZD6244, a specific inhibitor of MEK, in advanced HCC. The primary end point was response rate. The agent was administered orally at a dose of 100 mg twice a day. Despite the good tolerability, minimal activity was observed (no response, and stable disease in 37.5% of the patients). The median TTP was reported to be 8 weeks.

3.7 Immunomodulatory agents

Immunomodulation is another promising strategy against HCC. Thymostimulin (a standardized low molecular protein fraction containing thymosin-a1 and thymic humoral factor) has been demonstrated to induce a selective, dose-dependent, cytotoxic immune reaction against HCC cell lines in vitro. Based on the experimental data, two single-center phase II trials using thymostimulin in patients with locally advanced and metastasised HCC not amenable to or failing surgical and/or local therapy have been published, with 63% and

79%, respectively, both depicted tumor control rates even in metastatic disease and without side-effects. Both of them, however, lacked control groups.

Recently, a multi-center, randomised, placebo-controlled phase III study in HCC patients according to the same eligibility criteria with the studies reported above. Liver function (Child-Pugh classification) was used for stratification and subgroup analysis. The aim was to evaluate if the tumor control by thymostimulin observed in the phase II trials would translate into improved survival as compared with best supportive care and placebo. Thymostimulin was administered in a dose of 75 mg subcutaneously 5 days a week for one year. Twelve-month survival was 28% for the thymostimulin group and 32% for the control group with no significant differences in median OS (5.0 vs. 5.2 months)or TTP (5.3 vs. 2.9 months). Adjustment for liver function, Karnofsky status or tumor stage did not affect results. While quality of life was similar in both groups, fewer patients on thymostimulin suffered from accumulating ascites and renal failure (Dollinger et al., 2010).

3.8 Radioembolization

Attempts to improve locoregional therapies for patients with unresectable HCC are ongoing; as a result, novel liver directed therapies are emerging. Radioembolization is one such therapy, comprising a catheter-based delivery of yttrium-90 (90 Y)-embedded microspheres into the hepatic artery. Once administered, these microspheres selectively emit high-energy, low-penetration radiation to the tumor, resulting in necrosis. Currently, phase I and phase II studies are under way to evaluate the efficacy of this approach, and a number of cohort studies, retrospective analyses, and case reports have already been published. Indeed, a recent literature review showed that there is a growing body of literature to suggest that radioembolization might be an effective treatment approach for patients with HCC.

A phase II study evaluated radioembolization with 90 Y glass microspheres in patients with unresectable HCC with and without portal vein thrombosis. Treatment was well tolerated, with liver-related adverse events reported more frequently among patients with cirrhosis and main portal vein thrombosis (elevation of bilirubin, 40%; ascites, 18%; hepatic encephalopathy, 4%, compared with 4%, 4%, and 0%, respectively, for patients without main portal vein thrombosis or cirrhosis). Tumor response rates according to the World Health Organization and EASL criteria were 42.2% and 70%, respectively; median survival times for patients with main portal vein thrombosis and thrombosis were 304 days and 813 days for those without cirrhosis. These findings therefore suggest that treatment with 90 Y glass microspheres could be an effective locoregional treatment option, especially for patients with portal vein thrombosis, for whom TAE/TACE is not suitable. However, further evaluation of this novel approach, including direct comparisons with established locoregional therapies (i.e., TAE or TACE), is needed (Lencioni et al., 2010) .

3.9 Radiotherapy

Technological advances and a better understanding of partial liver tolerance of radiation therapy (RT) have improved our ability to deliver tumoricidal doses of RT safely to HCCs, and have led to a resurgence of interest in curative-intent treatment of HCC using RT.

3.9.1 Partial liver irradiation

The development of three-dimensional conformal RT has enabled high dose RT to be directed to the tumour while sparing the nontumour-bearing surrounding liver parenchyma from these high doses.

Using a mathematical model that predicts the risk of radiation-induced liver disease based on dose and fractional volume receiving a given dose, the probability of radiation toxicity can be minimized while still being able to escalate the dose to a small volume.

3.9.2 Image-guidance and targeting

Technological advances in RT now facilitate greater ability to account for respiratory movement of liver tumours during treatment. Tumors can be localized during breathing by using the diaphragm as a surrogate for liver position, via four-dimensional (4D) CT scanning to define the spatial coordinates of the tumour during all phases of respiration, via volumetric cone-beam CT scanning, or using radiopaque fiducials implanted in the vicinity of the tumour. Tumours can be treated during free breathing based on 4D CT derived composite target volumes (coordinates of the tumour during all phases of breathing) or via real-time tracking of tumour motion and gating or robotic control of the treatment beam, during breath holds using active breathing control, or during end-expiratory gating.

These techniques improve the precision of radiation delivery and thereby limit collateral normal tissue toxicity.

3.9.3 External beam radiation therapy

Promising clinical data from multiple studies suggest that HCCs are indeed radiosensitive. Sustained local control rates ranging from 71% to 100% have been reported following 30–90 Gy delivered over 1–8 weeks.

Combination of conformal RT (1.5 Gy twice daily over 6–8 weeks) with concurrent hepatic arterial fluorodeoxyuridine to treat HCCs safely to doses as high as 90 Gy, reported median survival of 15.2 months. Analysis of these data suggested that doses greater than 75 Gy resulted in more durable in-field local control than lower doses. In a prospective phase II trial 66 Gy in 33 fractions were administered to HCC patients ineligible for curative therapies and 92% tumour responses and 78% 1-year local control rates were noted.

With the use of higher doses and fewer fractions (hypofractionated RT), excellent local control rates ranging from 70% to 90% have been reported when the radiation beam can be directed from multiple planes (stereotactic RT) converging on the tumour, the majority of the liver can be spared from irradiation, and treatment is image-guided. Across all partial liver radiation paradigms, the most common site of first recurrence is intrahepatic, however outside the high dose-irradiated volume; toxicity is greater in Child-Pugh B compared to Child-Pugh A patients.

3.9.4 Proton irradiation

In contrast to photon irradiation, where the dose delivered to the tumour is limited by the entrance and exit doses that can potentially harm normal tissues, accelerated proton beams

deposit dose within the tumour without exiting through normal tissues beyond the tumour. With the administration of 72 Gy in 16 fractions of proton beam therapy in Japanese patients with unresectable HCC a 5-year local control rate of 87% and an overall survival rate of 23.5% in the absence of significant toxicity were noted. Furthermore, a 5-year survival rate of 53.5% was achieved in almost 25% of 50 patients with solitary tumours and Child-Pugh A cirrhosis suggesting that proton beam therapy is safe and efficacious in the treatment of HCC, and that the results may compare favorably to other curative treatments. Other groups have reported similar results with proton beam therapy of HCCs as well.

3.9.5 Combination of RT with other therapies

Tumours treated with TACE, an established treatment for unresectable HCC, often do not achieve durable local responses. RT has been combined with TACE to overcome treatment resistance. A greater than 60% response rates and a significant drop in tumour markers levels using this combination treatment strategy were noted . TACE followed by RT was reported to improve overall survival over TACE alone in a retrospective analysis of this experience. Similar results have been reported by other groups.

To address the persisting challenge of out-of-field intraheptic failures despite improved in-field local control, concurrent intra-arterial 5-FU and RT followed by monthly 5-FU and cisplatin has shown some promise (Schwarz et al., 2010)

4. Conclusion

Today, Sorafenib is the only approved systemic drug for the treatment of advanced HCC and is considered the new reference standard in the care of patients with this disease and preserved liver function. Several other molecular targeted agents are in different stages of clinical and preclinical development, or as single agents or in combinations.

The efficacy and safety of these agents is under investigation.

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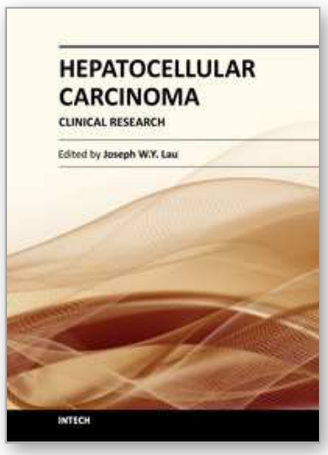

Hepatocellular Carcinoma - Clinical Research
Edited by Dr. Joseph W.Y. Lau

ISBN 978-953-51-0112-3
Hard cover, 330 pages
Publisher InTech
Published online 02, March, 2012
Published in print edition March, 2012

This book covers the clinical aspects of hepatocellular carcinoma. This book is a compendium of papers written by experts from different parts of the world to present the most up-to-date knowledge on the clinical aspects of hepatocellular carcinoma. This book is divided into three sections: (I) Diagnosis / Differential Diagnosis; (II) Surgical Treatment; (III) Non-surgical Treatment. There are 19 chapters covering topics from novel diagnostic methods to hepatic lesions mimicking hepatocellular carcinoma, from laparoscopic liver resection to major hepatectomy without allogeneic blood transfusion, from molecular targeted therapy to transarterial radioembolization, and from local ablative therapy to regional therapy. This volume is an important contribution to the clinical management of patients with hepatocellular carcinoma. The intended readers of this book are clinicians who are interested in hepatocellular carcinoma, including hepatologists, liver surgeons, interventional and diagnostic radiologists, pathologists and epidemiologists. General surgeons, general physicians, trainees, hospital administrators, and instruments and drug manufacturers will also find this book useful as a reference.

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