World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v2.i9.348

World J Gastrointest Oncol 2010 September 15; 2(9): 348-359
ISSN 1948-5204 (online)

TOPIC HIGHLIGHT

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Current approach in the treatment of hepatocellular carcinoma

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Received: January 12, 2010 Revised: August 24, 2010
Accepted: August 31, 2010
Published online: September 15, 2010

Abstract

Hepatocellular carcinoma (HCC) is the most common malignant hepatobiliary disease; it is responsible for about 1 million deaths per year. Risk factors include hepatitis B and C, hepatic cirrhosis, including alcohol related hepatitis, metabolic and nutritional hepatic damage. The main modality of diffusion is intrahepatic in the natural course of the disease. There are two leading types of treatment: local and systemic. Surgical resection and liver transplantation constitute the most appropriate local treatments and are considered the only real possibility for recovery. Other local approaches include: radiofrequency ablation, percutaneous ethanol ablation, hepatic endoarterial chemoembolization and intrahepatic radiotherapy (SIRT: selective internal radiation therapy). These last treatments are used to control the disease when surgery or transplantation is not achievable; in some cases they are able to prolong survival while they constitute mainly a palliative treatment. Systemic treatments include: chemotherapy, immunological and hormonal therapies and, more recently, the introduction of new specific molecular target drugs. At the moment, in this group, the only drug that has given positive results during phase Ⅲ trials (SHARP study) is Sorafenib. Sorafenib represents the only primary systemic therapy that has demonstrated, unlike the other treatments previously described, an increase in survival rate in patients affected with advanced HCC. Currently, other studies are taking place that are further developing the potential of this drug. These studies, including phase Ⅲ trials, are directed in order to test the activity and safety of new emerging drugs with targeted activity. Examples of these new agents are: Sunitinib, Gefitinib, Cetuximab, Bevacizumab and Erlotinib.

Key words: Systemic treatments; Hepatocarcinogenesis; Targeted therapy; Sorafenib; Hepatocarcinoma; Local treatments

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Rossi L, Zoratto F, Papa A, Iodice F, Minozzi M, Frati L, Tomao S. Current approach in the treatment of hepatocellular carcinoma. *World J Gastrointest Oncol* 2010; 2(9): 348-359 Available from: URL: http://www.wjgnet.com/1948-5204/full/v2/i9/348.htm DOI: http://dx.doi.org/10.4251/wjgo.v2.i9.348

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common malignant hepatobiliary disease and is responsible for about 1 million deaths per year. It is more common in males and represents the 5th most frequent neoplastic disease. HCC

globally accounts for 4.6% of all neoplasias and has a mortality rate of 94%. The mean age of diagnosis is between 50-60 years[1].

Risk factors include hepatitis B and C, hepatic cirrhosis, including alcohol related hepatitis[2]. There is evidence that hepatitis B is the main cause for the onset of HCC[3] and most hepatitis B virus (HBV) infections occur during infancy and the perinatal period, especially in developing countries; often it tends to become a chronic disease. In developed countries, the infection manifests later and is associated with viral elimination. A chronization of a primary infection determines an increase of 100 times of the oncogenic potential of the virus compared to subjects whose infection does not become chronic. Chronic hepatitis B in 80% of cases is associated with HCC. Instead, in the majority of cases, HCC is not associated with HBV and is very often responsible for the onset of hepatocarcinoma in Europe, Japan and North America.

Another important risk factor responsible for the development of HCC is hepatitis C correlated cirrhosis that often manifests 20-30 years after the viral infection. The median age of HCC onset associated with HBV infection is 52 years while it is 62 years in those cases associated with the hepatis C virus (HCV). Therefore, it appears reasonable that the carcinoma associated with the HCV progresses more rapidly. In the case of a coinfection with both viruses, cirrhosis evolution is faster and the risk of related HCC is increased.

Ethanol related cirrhosis, chronic autoimmune hepatitis and idiopathic cirrhosis are all correlated with an increased HCC risk. In fact, alcohol abuse, especially if chronic, determines alcoholic hepatopathy and cirrhosis with a consequent increased risk of HCC development[4]. Geographical differences exist in the incidence of HCC correlated to the exposition of other cancerogenic factors such as aflatoxin B which is produced by the fungus Aspergillus Flavus and can contaminate certain foods[5]. This can be observed more frequently in developing nations where food conservation is poorer.

NATURAL HISTORY

The natural history of the disease is characterized mostly by an intrahepatic spread; it can manifest itself with single or multiple neoplastic sites with infiltration of the hepatic ducts or of the portal vein with portal thrombosis. These events determine a poorer prognosis[6]. If extrahepatic infiltration is present, central lymph nodes are usually interested. Extrahepatic metastases are rare and usually involve the bones (20%). The initial symptoms of HCC in 90% of cases are acute or chronic pain located in the right hypochondrium and epigastrium which tends to increase with the progression of disease. It is possible to observe an increase in abdominal size caused by the hepatic mass and the presence of ascites. In some cases, jaundice may be present as a result of liver failure; less frequently it is caused by compression of the bile ducts. In this parade of symptoms, paraneoplastic syndromes may also be present and include hypoglycemia, erythrocytosis, hypercalcemia, hypo-hypercholesterolemia and gynecomastia.

LOCAL TREATMENTS

Surgery

Surgery is the treatment of choice for HCC. The percentage of resectability of this tumor at the moment of diagnosis is about 20%-30%. This percentage constitutes the lowest resection rate among all abdominal tumors, mainly due to the fact that surgical treatment depends on variables that are associated with the tumor itself and the chronic hepatopathy that is often linked with the hepatocarcinoma.

Other important variables associated with the tumor and that must be evaluated include focal length, location and size. However, from a resectability point of view, the patient affected by hepatocarcinoma must have a normal liver function including healthy surrounding liver tissue, suggestive of a significant regenerative potential; this is essential to allow functional resections of 60%-70%. In fact, a cirrhotic liver loses its regenerative potential and has less functional reserve and therefore these two characteristics greatly limit the possibility of complete surgical resections.

Generally, most hepatocellular carcinomas originate from cirrhotic livers and, in this case, the Child-Pugh classification is the most reliable method for classifying patients eligible for surgical treatment, especially those belonging to group A[7].

Hepatic hemodynamic tests can provide useful elements for preoperative evaluation. According to Bruix, patients eligible for surgical resection are those with a good functional reserve (Child A), a single HCC nodule with a diameter < 5 cm and a pressure gradient inside the portal vein less than 10 mmHg[8]. Contraindications are portal thrombosis, elevated bilirubin levels > 1 mg/dL, Child class B and C, lymphonodi metastases, extrahepatic localization of the hepatocarcinoma or a multifocal nature[9].

In a case of hepatocarcinoma that arises from a normal liver, surgical resection is the treatment of choice, especially if the lesion is superficial and of small dimensions[10].

In conclusion, surgical treatment is the gold standard for tumors of small dimensions and patients with a good functional liver reserve while liver transplantation is indicated for patients with a compromised hepatic function[11]. The mean survival of patients with hepatocarcinoma after radical surgical treatment is 69% at 1 year, 35% at 3 years and 21% at 5 years. Postoperative mortality varies between 3 and 20% depending on the characteristics of the tumor, the presence of cirrhosis and the experience of the surgical team.

Transplantation

Hepatocarcinoma is the only solid tumor where transplantation plays an important role; in fact it represents a potential therapeutic option in patients with cirrhosis and hepatocarcinoma. This is due to the fact that this method allows the removal of the primary tumor and treats hepatic insufficiency by removing cirrhotic tissue simultaneously[12].

During recent years, the indications for liver transplantation in this group of patients have changed and today the approved criteria are those that take into consideration parameters such as dimensions and number of hepatocarcinoma nodules.

The main inclusion criteria followed are those of Milano that consider patients with HCC to be eligible for liver transplantation if there is a single hepatic lesion with maximum dimensions of 5 cm or there are three hepatic lesions with a maximum diameter less than 3 cm[13].

In conclusion, patients affected by HCC with dimensions less than 5 cm or 3 nodules inferior to 3 cm (therefore according to the Milano criteria) treated in specialized liver transplantation centers can reach a survival rate at 5 years of 70% with a risk of recurrence less than 15%[12,13]. The presence of vascular invasion is considered as one of the most accurate predictive factors for survival and recurrence risk. Another crucial point is that the best results are obtained when the transplant waiting time is less than 6 mo; however this aim is rarely achievable due to the lack of organ donors. Systemic and local treatments are used as transplantation bridges in patients waiting for organ donation in order to control the disease and prevent possible metastases[14].

Percutaneous ablation and radiofrequency

Patients who are inoperable due to the presence of comorbidities and insufficient liver function reserve can be considered candidates for percutaneous ablation. Ablation can be obtained using either chemical (alcoholization) or physical methods (radiofrequency-RFA). Both alcoholization and radiofrequency can be used in patients that are on the transplantation list awaiting organ availability. Liver transplantation is the ideal treatment in patients with HCC and cirrhosis; however its application is limited because of the limited number of donors and, consequently, organs available[15].

This technique has shown an increase in survival in patients with advanced HCC; however the superiority of this procedure in comparison with surgical intervention has still to be proven[16]. RFA utilizes elevated frequency alternated currents through an electrode inserted directly into the tumor causing necrosis-thermal coagulation. In a-2.5 cm tumor, a necrosis of 80% could be obtained. The frequency of local recurrence after RFA of HCC is low when the tumor is smaller than 2.5 cm or in the case of nodular type HCC with no localization in the perivascular spaces[17]. When a small tumor is detected, RFA is an alternative to resection for the treatment of HCC. The main advantages compared to surgical intervention are less invasiveness and the increased possibility of parenchymal sparing[18,19].

Percutaneous ablation is considered the best treatment for patients with early-stage HCC who are not candidates for surgical resection. Over the years, various methods have developed including PAI (intratumoral injection of ethanol or acetic acid) and radiofrequency thermal ablation, laser and microwaves. Percutaneous ethanol injection (PEI) has for many years been considered the most appropriate technique utilized. Several studies have shown that the PEI impacts on the natural history of HCC. The major limitation of PEI is the high incidence of local recurrence which is between 33%-43%. Recent studies have shown that the use of RFA compared to PEI could guarantee a better control of the disease. In a randomized study, there was a higher local recurrence free survival rate in patients treated with RFA compared to patients treated with PEI. Further studies are needed to assess whether the same effect is also confirmed during the intermediate stages[20].

RFA is superior to PEI in terms of overall survival and local recurrence rates for patients with cirrhosis Child-Pugh class A or B and early unresectable HCC. Interestingly, the survival advantage increases with time[21,22].

Hepatic arterial chemoembolization

Hepatic arterial chemoembolization (TACE) is now one of the most common treatments for unresectable hepatocarcinoma[23]. Typically, hepatocarcinoma nodules are highly vascularized with arterial afferents originating from the hepatic artery. The main indications for TACE are represented by surgically unresectable tumors with reference to: (1) Multiple nodules involving both liver lobes; (2) Multiple nodules involving only the right liver; (3) Single nodule in a patient with a high operative risk; (4) Single nodule in a patient who refuses "open" surgery; and (5) Single nodule that "overlaps" the two liver lobes. The main contraindications to TACE are represented by diffuse forms of cancer-cirrhosis, extended portal vein thrombosis and decompensated liver cirrhosis.

This technique is performed under local anesthesia with incannulation of the femoral artery at the groin. From this access and with special catheters, the hepatic artery can be reached; moreover by injecting a contrast medium we can obtain a radiological visualization of the distribution of the hepatic arteries and an accurate diagnosis of hepatocellular carcinoma. This type of treatment, contrary to what occurs in traditional chemotherapy, allows the maximum drug concentration within the lesion and minimum in surrounding organs.

In fact, through an angiographic catheter placed inside the arteries that supply blood to the tumor nodules, a solution of soluble contrast medium (lipiodol) and specific chemotherapy drug (epirubicin, doxorubicin, cisplatin) can be infused. With this approach a permanent chemical closure of the arteries occurs and therefore the chemotherapeutic agent acts at intratumoral level for a long time because it is confined within the tumor nodule and is not washed away by the bloodstream[24].

Special particles of various sizes (from 100 to 1000 microns) can be used with the characteristic not only of embolizing the tumor but also of releasing substances over time (up to 30 d) that determine antiblastic necrosis.

Hepatic arterial chemoembolization has demonstrated good results for local disease control in patients who are not candidates for surgical treatment and has minimal side-effects thanks to the ability to treat the lesion locally without the necessity to use more toxic systemic chemotherapy[25]. However, this approach appears to confer no significant difference in terms of overall survival for

patients treated with exclusive hepatic arterial embolization[26,27].

Selective internal radiation therapy

Intrahepatic radiotherapy, better known by the acronym selective internal radiation therapy (SIRT), is a therapy based on the local intra-arterial administration of Yttrium 90. This radionuclide is a pure beta radiation emitter, has a half life of 64 h and is produced by nuclear bombardment of the species stable Yttrium 89. Yttrium is transported into the hepatic artery by inert beads with a diameter of 35 micrometers, a size that allows the radioactive particles to pass through the vascular network of the liver and reach the finest peripheral capillaries. Here the beads come into contact with tumor cells which are hit by radiation emitted by the radioisotope. The effect of yttrium takes about 10 d then irradiated cells undergo necrosis and within one month after surgery, the liver remains as a single scar.

SIRT is a minimally invasive technique; the procedure is in fact carried out under local anesthesia. The process of release of the microspheres occurs by using a flexible catheter inserted into the femoral artery which is moved forward by the radiologist until the hepatic artery is reached.

It is a new treatment for liver cancer and liver metastases originating from colorectal carcinoma. Radiation used in the treatment of various types of neoplasias indiscriminately also destroys healthy cells but in this case the action is specific and is localized only in the liver; the tumor cells are vascularized mainly by the hepatic artery meanwhile the other cells are vascularized by the portal vein. With SIRT there is a direct entrance of the radioisotope into the hepatic artery; in fact the radiation has a destructive action on tumor tissue sparing the rest of the organ.

In terms of toxicity, most patients have not reported any major side effects; in a small percentage, an elevation of liver enzymes, fatigue and fever have been reported. However, in most cases it is a well tolerated therapy.

SIRT represents a new therapeutic option for patients with unresectable hepatocellular carcinoma and the first clinical studies seem to demonstrate an increase in terms of survival rate when using this technique in combination with systemic chemotherapy. In addition, the use of SIRT tends to reduce the size of the tumor and allows some patients to become eligible for surgical resection. Finally, it appears to have positive effects on survival with an average of 23 and 11 mo respectively in patients of grade I and II according to the Okuda classification[28-30]. In conclusion, although the indications for SIRT are still a topic for discussion, this appears to be a valid alternative in disseminated and multifocal liver tumors[31].

SYSTEMIC TREATMENTS

Chemotherapy, immunological and hormonal treatments

Chemotherapy with cytotoxic agents such as doxorubicin, cisplatin or 5-fluorouracil showed a low response rate (< 10%) without a clear benefit in overall survival[32]. Moreover, chemotherapy is poorly tolerated in patients with this type of pathology, especially since both cirrhosis and liver failure may have an unpredictable course. In addition, these drugs have a hepatic metabolism mainly causing the toxicity of these drugs difficult to manage. No benefit has been demonstrated for interferon therapy[33], anti-androgens or tamoxifen used in the past in the treatment of advanced HCC with contradictory results[34].

Targeted therapy

In recent years, knowledge regarding the biological processes of hepatocarcinogenesis has expanded significantly allowing the identification of the molecular processes involved in the onset of this neoplastic disorder. Among these molecules, growth factors and neoangiogenesis factors with their receptors, tyrosine kinase intracellular enzymatic pathways and intracellular signal transmission factors have been identified. All of these substances represent potential molecular targets of the so called targeted therapy. These therapies consist largely of tyrosine kinase inhibitors and monoclonal antibodies which represent promising drugs for the treatment of advanced HCC.

Enzymatic pathways, growth factors and angiogenic processes involved in hepatocarcinogenesis: There are many pathways identified in the process of enzymatic activation of intracellular signals important for growth and proliferation of HCC. Among these pathways, the most frequently identified are the Ras/Raf/MEK/ERK (MAPK) pathway, phosphoinositol 3-kinase (PI3K) and the Wnt/catenin pathway. Major intracellular enzymatic pathways are involved in the process of hepatocancerogenesis; and the enzymatic cascade activated by the binding of epidermal growth factor (EGF) to its receptor is highlighted in particular (Figure 1).

Concerning the factors/receptors and angiogenic growth, the most important in the process of hepatocarcinogenesis are vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and EGF[35-40].

HCC is a highly vascularized tumor that requires the formation of numerous blood vessels to receive sufficient blood supply to grow and proliferate. Consequently, angiogenesis is a crucial process in the development of HCC[41,42]. VEGF represents the main mediator of this process; in HCC it is overexpressed with its receptor VEGFR[42-44]. High levels of VEGF correlated with a higher density of microvessels; therefore angiogenic activity and tumor progression are factors that worsen the prognosis[42,45,46]. Its effects are mediated by the interaction with the receptor tyrosine kinases VEGFR 1, 2 and 3 which are located on endothelial cells[47].

Other factors relevant to neoangiogenesis are PDGF and basic fibroblast growth factor (bFGF).

The EGF receptor family plays a crucial role in the proliferation of HCC[48]. EGFR is frequently expressed in HCC and its overexpression has been shown to be an independent negative prognostic factor for early tumor development and extrahepatic metastases[49-51].

The MAPK enzymatic pathway, often hyperactive in HCC[52-54], includes a cascade of enzymatic processes which are involved in the phosphorylation of four major kinases: ras, raf, mitogen-activated protein extracellular

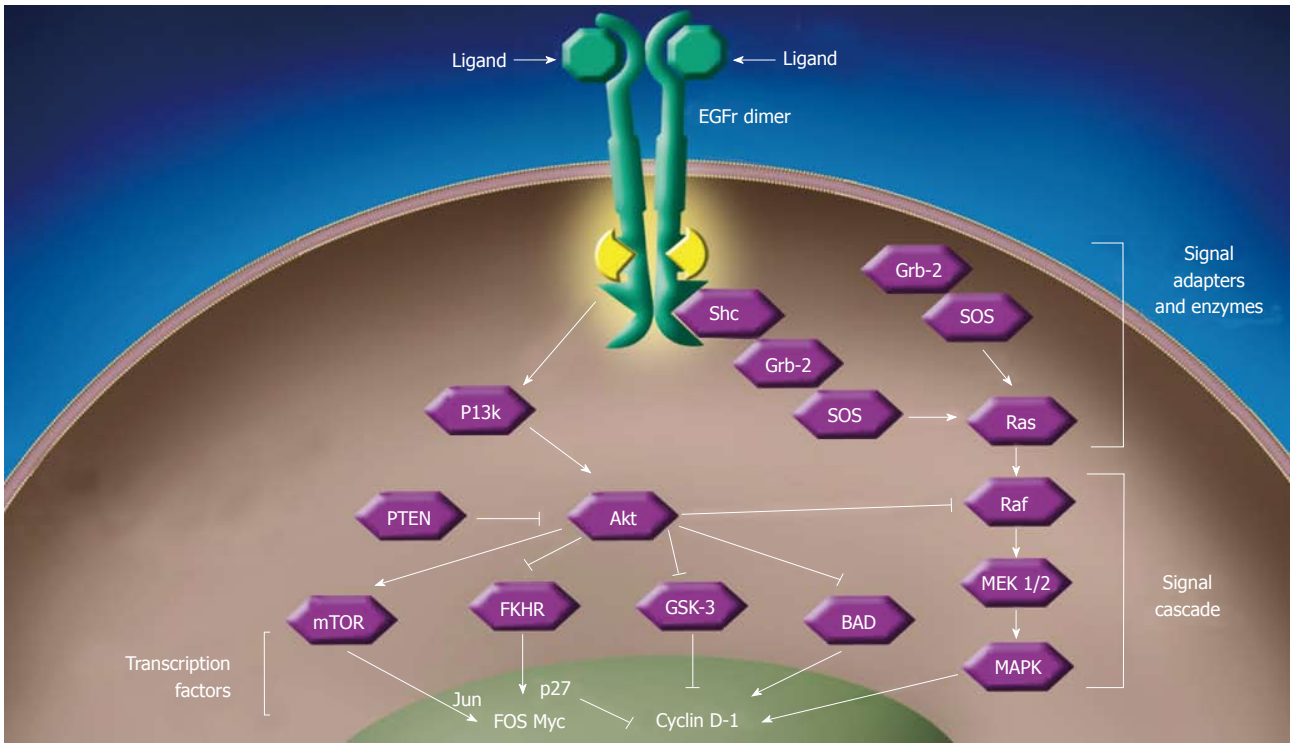

Figure 1 Hepatocancerogenesis. MAPK: Mitogen-activated protein kinase; P13k: Phosphatidylinositol 3-kinase.

kinase (MEK) and extracellular signal-regulated kinase (ERK)[55]. hepatocytes growth factor (HGF), VEGF and PDGF among others activate this pathway and induce the transcription of genes of AP-1 family as c-fos and c-jun, both involved in the proliferation and differentiation of HCC[56]. Finally, the pathway PI3K/Akt/mTOR which is located downstream of several receptor tyrosine kinases such as EGFR, is activated; this receptor is over activated in a subset of patients with HCC and controls cell proliferation, the cell cycle and apoptosis[57,58]. PI3K is partially regulated by PTEN (tumor suppressor phosphatase and tensin homolog) which is frequently mutated in HCC[59].

The activation of PI3K in turn activates Akt that phosphorylates and inactivates various antiapoptotic proteins.

An enzyme regulated by Akt is mTOR, a protein that plays a central role in cell proliferation and tumor angiogenesis[60], and is activated in a subset of patients with HCC; it represents a promising target for new drugs such as rapamycin, an inhibitor of mTOR[61,62].

All enzymes, receptors and proteins described above represent only a small fraction of the many molecular processes that occur in tumor cells of HCC which are unfortunately still largely unknown. However, what we currently know of such processes has allowed the testing of new drugs, the so called targeted therapy.

Clinical studies on molecular therapies in advanced hepatocellular carcinoma

Sunitinib is the only drug that phase Ⅲ clinical trials have shown its efficacy in the treatment of advanced HCC. All other molecular targeted therapies are now being evaluated in clinical phase Ⅰ or Ⅱ trials and some of them are preparing for Phase Ⅲ clinical studies to clarify their real efficacy in the treatment of this malignancy. Table 1 lists the phase Ⅲ trials of sunitinib and the main phase Ⅱ studies completed for these new molecules.

Sorafenib

Sorafenib is a multikinase oral inhibitor that works by electively blocking molecules belonging to two classes of kinases which are involved in the cellular proliferation of tumor angiogenesis. These kinases include Raf kinase, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-B, KIT, FLT-3 and RET[63,64]. Preclinical models have shown that the pathway Raf/MEK/ERK plays an important role in hepatocellular carcinoma and blocking the translation of the signal through Raf-1 may offer a therapeutic benefit in patients with this malignancy[65,66].

Sorafenib was approved in 2005 for the treatment of patients with advanced renal cell carcinoma[67,68]. The results of a phase Ⅱ study conducted on 137 patients with advanced hepatocellular carcinoma, Child-Pugh class A or B showed that sorafenib 400 mg × 2/d could have a therapeutic benefit in this type of cancer. The results of this study showed a median survival of 9.2 mo, median time to progression of 5.5 mo and disease stability > 4 mo in 33.6% of patients (radiological assessment)[69]. Based on this result, a phase Ⅲ study was conducted, SHARP (Sorafenib HCC Assessment Randomized Protocol), which led to EMEA and FDA approval of this drug for the treatment of HCC in October and November 2007, based on preliminary data presented for the first time at ASCO in June 2007[70,71].

The sharp is an international phase Ⅲ study conducted

Table 1 Sunitinib studies

Ref.	Molecule	Phase	Patients	RR	DS	PFS (mo)	TTP (mo)	OS (mo)
Abou-Alfa *et al*[69]	Sorafenib	II	137	2.2	33.6	nr	4.2	9.2
Llovet *et al*[70,71]	Sorafenib	III	602	2	71	nr	5.5	10.7
Cheng *et al*[72]	Sorafenib	III	226	3.3	54	nr	2.8	6.5
Richly *et al*[73]	sorafenib/doxorubicin	I	18	6	63	nr	nr	nr
Abou-Alfa *et al*[74]	sorafenib/doxorubicin	II	96	4	77	6.9	8.6	13.7
Siegel *et al*[86]	bevacizumab	II	46	13	nr	6.9	nr	12.4
Malka *et al*[87]	bevacizumab	II	30	12.5	54	nr	nr	nr
Zhu *et al*[88]	bevacizumab/GEMOX	II	33	20	27	5.3	nr	9.6
Sun *et al*[89]	bevacizumab/CAPOX	II	30	11	78	5.4	nr	nr
Hsu *et al*[90]	bevacizumab/capecitabine	II	45	9	42	4.1	nr	10.7
Thomas *et al*[92]	erlotinib	II	40	0	43	3.1	nr	6.25
Philip *et al*[93]	erlotinib	II	38	9	50	3.2	nr	13
Thomas *et al*[91]	bevacizumab/erlotinib	II	40	25	42.5	9.0	nr	15.6
O'Dwyer *et al*[94]	gefitinib	II	31	3	22.5	2.8	nr	6.5
Ramanathan *et al*[95]	lapatinib	II	30	5	35	2.3	nr	6.2
Zhu *et al*[101]	cetuximab	II	30	0	17	1.4	nr	9.6
Grünwald *et al*[102]	cetuximab	II	32	0	44	nr	1.9	nr
Asnacios *et al*[103]	cetuximab/GEMOX	II	45	20	40	4.7	nr	9.5
Faivre *et al*[81]	sunitinib	II	37	2.7	35	nr	5.3	9.3
Zhu *et al*[82]	sunitinib	II	34	2.9	47	4.0	nr	9.9
Hoda *et al*[83]	sunitinib	II	23	6	35	nr	nr	nr

RR: Response rate (complete + partial response), SD: Stable disease; PFS: Progression-free survival; TTP: Time to progression; OS: Overall survival; nr: Not reported; GEMOX: Gemcitabine + oxaliplatin; CAPOX: Capecitabine + oxaliplatin.

in 602 patients (with HCC in advanced cirrhosis Child Pugh A, ECOG PS 0,1,2); it is a randomized double-blinded, placebo-controlled trial whose main objective was to assess overall survival and progression time in symptomatic patients who received sorafenib compared to patients who received placebo. Secondary objectives included time to progression, the rate of disease control and tolerability. The study was interrupted after an interim analysis that showed a statistically significant advantage in overall survival in patients treated with sorafenib[71]. Patients who received sorafenib had a median survival of 10.7 mo against 7.9 mo in the placebo group [hazard ratio (HR) = 0.69, $P = 0.0006$] (Figure 2). There were no marked differences between the two groups in terms of symptomatic progression which was assessed by the administration of a self-assessment questionnaire. The median time to progression was 5.5 mo with sorafenib compared with 2.8 mo with placebo (HR = 0.58, $P < 0.001$). Overall, sorafenib reduces the absolute risk of death by 31% in patients with inoperable HCC or hepatic tumor compared to patients taking placebo. This represents a 44% increase in survival for patients treated with sorafenib (HR = 0.69, $P = 0.0006$). A separate analysis showed that tumor progression was slower in patients who received sorafenib compared to patients who received placebo.

The most common adverse reactions observed in patients treated with sorafenib were: fatigue, weight loss, rash or superficial skin desquamation, hand-foot skin reaction, hair loss, diarrhea, anorexia, nausea and abdominal pain. Twenty percent or more of patients experienced at least one of these reactions. In patients with hepatocellular carcinoma, diarrhea was reported in 55% of patients who received sorafenib. In 27% of patients treated with sorafenib, an inadequate blood flow to the heart or myocardial infarction was observed compared to 1.3% of patients who received placebo. Hypertension had an incidence of 9% among patients treated with sorafenib compared to 4% of patients in the placebo group. Forty percent of patients who received sorafenib presented an elevation of serum lipase compared to 37% of patients treated with placebo. Hypophosphataemia occurred in 35% of patients in the sorafenib group and 11% of those who received placebo. A second important phase III randomized, placebo-controlled double-blinded study was conducted by researchers in East Asia to assess the safety and efficacy of sorafenib in patients with unresectable or metastatic HCC. Two hundred and twenty six patients were randomized to sorafenib ($n = 150$) or placebo ($n = 76$)[72]. The overall median survival was 6.5 mo (95% CI: 5.56-7.56) in the group receiving sorafenib and 4.2 mo (3.75-5.46 mo) in the placebo (HR = 0.68, 95% CI: 0.50-0.93, $P = 0.014$). The median TTP was 2.8 mo in the group treated with sorafenib and 1.4 mo in the placebo (HR= 0.57; 95% CI: 0.42-0.79, $P = 0.0005$). A PR was observed in 3.3% of patients and 54% achieved SD. In contrast to the SHARP study, the toxicities G3/4 most frequently observed were: the hand-foot syndrome (10.7%), diarrhea (6%) and fatigue (3.4%).

Another randomized, double-blind phase II trial on 96 patients with advanced HCC evaluated sorafenib efficacy and doxorubicin versus doxorubicin plus placebo showed encouraging results (TTP 8.6 mo *vs* 4.8 mo and OS 13.7 mo *vs* 6.5 mo)[74]. This association needs to be better evaluated and studied in future phase III studies[75,76].

Sorafenib reduces the levels of HGF and increases those of VEGF, two markers associated with a decreased survival in patients with HCC. Sorafenib reduces the levels of c-Kit by 33%, of HGF by 7.4%, of sVEGFR-2 by

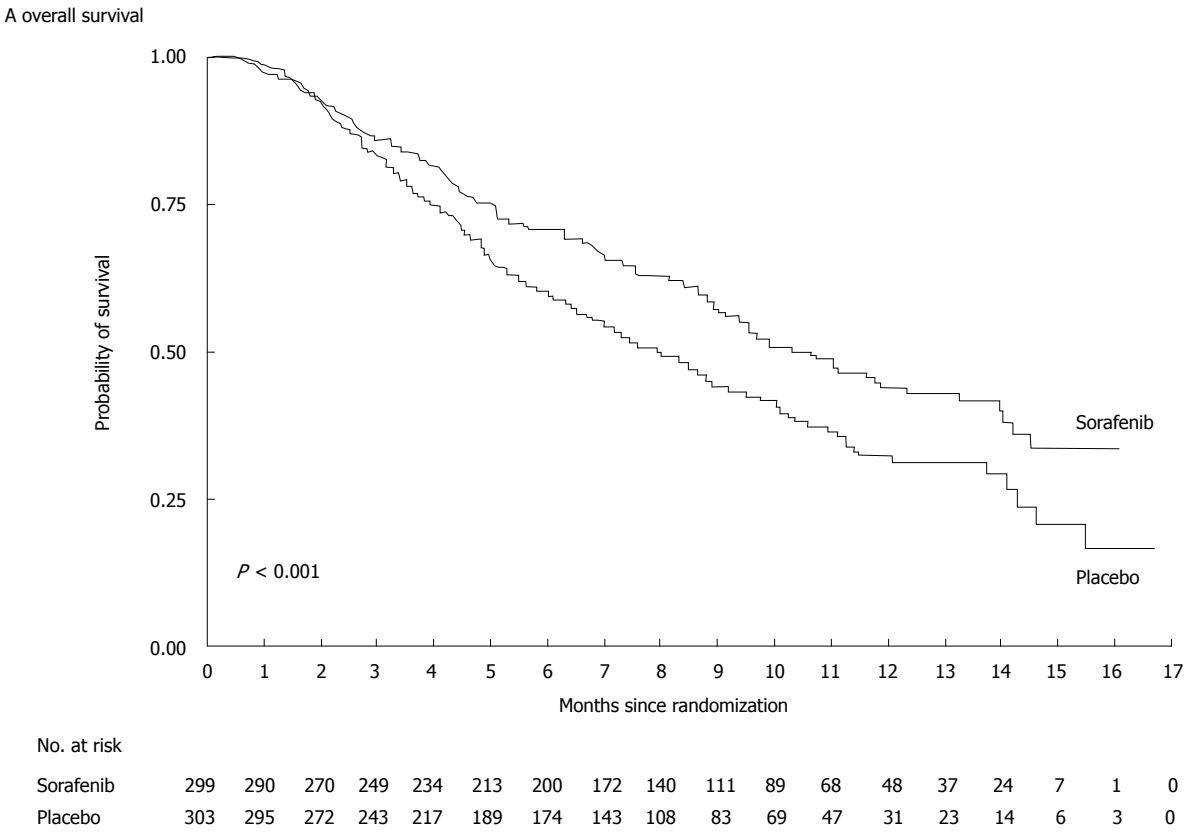

Figure 2 In sorafenib group median survival is 2.8 mo longer than placebo group (HR = 0.69, *P* = 0.0006)[71].

25.7% and sVEGFR-3 by 14.1% and doubles the levels of VEGF. Low levels of HGF and c-Kit have been associated with a longer survival in patients treated with sorafenib[77].

The main criticism of the SHARP study was that it was conducted in patients with Child-Pugh class A and thus with well preserved liver function. The authors' response was that the inclusion of patients with advanced liver dysfunction (class B-C-Child Pugh) could have masked the efficacy of Sorafenib due to the presence of several deaths caused by advanced cirrhosis. Further studies are necessary to confirm the efficacy of the drug in patients with medium and severe hepatic insufficiency. In addition, treatment with sorafenib is associated with less severe complications than those seen with other systemic therapies such as the pattern PIAF (cisplatin, interferon, doxorubicin and 5-fluorouracil)[33].

Sorafenib is therefore now part of the treatment algorithm for advanced HCC (Figure 3).

Sunitinib

Sunitinib malate is an oral multikinase inhibitor approved for the treatment of GIST after progression or intolerance to imatinib mesylate[78] and also for the treatment of advanced or metastatic kidney cancer[79]. Sunitinib works by blocking the activity of several tyrosine kinase receptors such as VEGFR-1/2 and PDGFR, c-Kit, Flt-3 and RET[80]. Sunitinib has been shown to possess antitumoral activity and an acceptable safety profile in several Phase Ⅱ trials in patients with advanced HCC[81-83]. However, it appears to have a higher toxicity with a greater number of side effects in patients with HCC compared to studies of patients affected by other neoplastic diseases.

For this reason, the dose usually used in studies of HCC is 37.5 mg rather than 50 mg. For example, in a phase Ⅱ study on 37 patients, the original starting dose was 50 mg/d for 4 consecutive weeks followed by two rest periods[81]. The main grade G3/4 toxicities observed were thrombocytopenia (43%), neutropenia (24%), neurological symptoms (24%), fatigue (22%) and hemorrhages (14%). Forty-three percent of patients required a dose reduction. Four patients died due to the treatment. Median TTP was 5.3 mo and OS was 9.3 mo.

A second 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[80]. Grade 3/4 toxicities observed were GOT (18%) and GPT (9%), 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. SD was highlighted in 47% of patients for at least 12 wk. PFS was 4 mo and the median OS of 9.9 mo.

A third study involving 23 patients with the schedule 37.5 mg/d, 4 wk on/2 off showed similar results with regard to radiological response (PR = 6%, SD = 35%) and toxicity[83].

Based on these data, phase Ⅲ trials are beginning in

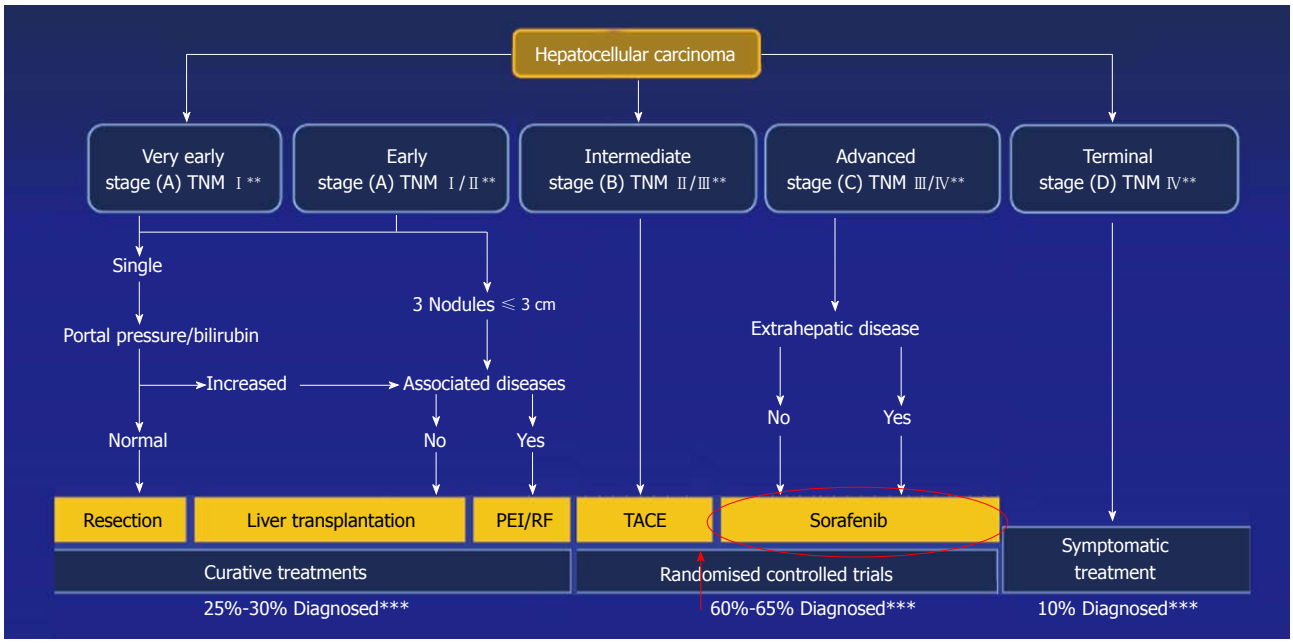

Figure 3 Algorithm for treatment of hepatocellular carcinoma.

order to better assess the effectiveness and toxicity of sunitinib.

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody directed against VEGF and is now a key drug in the treatment metastatic colon-rectum carcinoma[84]. It possesses antiangiogenetic activity and thus inhibits neovascularization and tumor growth by enhancing the activity of chemotherapeutic agents[47,85]. Bevacizumab has been used in several Phase I-II trials in the treatment of advanced HCC, either as a single agent[86,87] or in combination with chemotherapeutic agents such as oxaliplatin/gemcitabine[88] or with capecitabine/oxaliplatin[89,90]. As a single-agent, response rates of around 13% have been observed; in combination with oxaliplatin/gemcitabine response rates of 20% were seen with a SD of 27%. With the association capecitabine and oxaliplatin, a PR of 11% and a SD of 78% were obtained, showing encouraging results.

A recent study by Thomas *et al*[91], discussed later, assessed the use of bevacizumab in combination with erlotinib. This study showed good results.

The use of Bevacizumab, however, is responsible for important toxic side effects, especially in terms of bleeding and thromboembolic events which require further evaluation.

Erlotinib and other anti-epidermal growth factor receptor drugs

Erlotinib[91-93], gefitinib[94] and lapatinib, tyrosine kinase inhibitor drugs with activity against 1 and 2 EGFR[95], are approved for the treatment of non-small cell lung cancer[96] and breast cancer[97] and have been evaluated in several phase Ⅱ studies in advanced HCC.

Two phase Ⅱ studies have tested erlotinib 150 mg/d used as a single agent. The two studies showed mixed results in terms of survival (10.75 mo *vs* 6.2 mo respectively) and response rate and did not demonstrate any antitumoral activity[92,93].

However, a recent study by Thomas *et al*[91] evaluated the use of bevacizumab in combination with erlotinib in 40 patients, suggesting a synergistic effect of both drugs. A PR of 25%, a PFS of 9 mo and an OS of 15.65 mo were obtained. Toxicity of grade 3/4 was: fatigue (20%), hypertension (15%), gastrointestinal bleeding (12.5%), diarrhoea (10%), increased GOT/GPT (10%) and thrombocytopenia (2.5%). These data should be interpreted with caution while the results of phase Ⅲ trials are pending[98].

With regard to toxicity, a key point is represented by the use of bevacizumab in patients with portal hypertension. Gefitinib (PFS = 2.8 mo, OS = 6.5 mo)[94] and Lapatinib (PFS = 2.3 mo, OS = 6.2 mo)[95] have shown modest activity in advanced HCC.

Cetuximab is a chimeric monoclonal antibody (human and murine) directed against EGFR, approved for the treatment of squamous cell carcinoma of the head and neck[99] and metastatic colorectal cancer[100]. Cetuximab has been evaluated as a monotherapy in patients with advanced HCC in two phase Ⅱ studies[101,102]. Furthermore, it has been tested in phase Ⅱ studies with gemcitabine and oxaliplatin[103]. However, no significant activity with ceftuximab as a monotherapy was demonstrated and only a modest activity was seen in combination with chemotherapy.

New drugs

Traditional chemotherapeutic agents were investigated for many years in the treatment of advanced hepatocellular cancer without confirmation of proven activity. Therefore in the scenario of targeted therapy now, several new drugs with targeted activity are currently being evaluated in phase I and Ⅱ trials for the treatment of advanced HCC

such as Vatalanib[104], Cediranib[105], bortezomib (a proteasome inhibitor)[49]. At the moment, the data are inconclusive and more extensive studies are necessary to test and to validate the activity of these novel agents against hepatocellular cancer.

CONCLUSION

Sorafenib certainly represents a novelty in the treatment of advanced hepatocarcinoma. The first results are encouraging considering that the incidence of HCC worldwide has increased[8] and other treatments that have been evaluated in the last thirty years in 100 randomized control trials have shown little influence in the overall survival rate[27,106,107]. New studies are underway to evaluate new schedules of drug administration, particularly in combination with chemotherapy to try to obtain an increase in response to treatment without causing an excess of toxicity which has to be considered unacceptable for the patient. Further studies are also needed to assess the effectiveness of sorafenib in the adjuvant treatment of HCC and possibly in combination with surgery and other regional treatments. Innovative and specific biomolecular and enzymatic evaluations should also be used to attempt to identify subpopulations of patients who may benefit from a greater or lesser degree of treatment with sorafenib and other drugs. Furthermore, new molecules (erlotinib, bevacizumab, gefitinib, sunitinib) are being tested in clinical trials of phase II to assess their likely effectiveness, alone or in combination in the treatment of HCC.

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