ANNALS OF GASTROENTEROLOGY 2008, 21(2):83-87

Current View

New developments in systemic therapy for hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) accounts for 90% of all primary liver cancers. HCC is the fifth most common malignancy and the third cause of cancer death globally (more than 500.000 cases yearly) with most deaths occurring within one year of diagnosis.[1,2] In 90-95% of cases, HCC is developed in cirrhotic liver. Liver transplantation (from cadaveric or living donors), surgical resection, percutaneous ethanol injection, transcatheter arterial chemoembolizatin (TACE) and radio-frequency (RF) thermal ablation microwaves achieve a relatively high response rate only in carefully selected candidates with small (diameter < 5 cm) tumors. Hepatic reserve often dictates the therapeutic options. Systemic therapy is appropriate for patients with advanced unresectable disease who are unsuitable for locoregional therapy and carry dismal prognosis. Nevertheless, up until now, there have been multitudes of negative systemic therapy trials for advanced HCC.[3] So, in 60-75% of HCC cases in Europe and the USA, no therapy short of palliative approaches was given to patients.[4,5,6,7]

Since estrogen receptors (ERs) are present in approximately one-third of HCCs, these tumors could potentially benefit from ER blockade with megestrol[8] or tamoxifen.[9,10] Nevertheless, several prospective randomized trials and a systematic review of tamoxifen in patients with advanced HCC have failed to show a survival benefit or improved functional status.[11] One possible reason for the lack of efficacy may be the presence of variant ERs in HCC.[12] Chemotherapy has not demonstrated any benefit for the addition of tamoxifen.[10]

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Somatostatin receptors has been identified in liver tissue from patients with HCC.[13,14] The administration of octreotide as monotherapy, in patients with advanced HCC, has achieved controversial results.[15,16,17] Recently, long-acting octreotide (Sandostatin LAR, 30 mg intramuscularly, every 4 weeks) has shown to improve the survival and quality of life in somatostatin receptors positive patients with advanced HCC.[18] No α_1 fetoprotein (AFP) reduction and decrease of the tumor mass or the number of the satellite sites were observed. The statistically significant survival benefit for the octreotide group was attributed to a slower tumor progression or/and inhibition of angiogenesis and proliferation or/and induction of apoptosis of HCC cells. At the present time, routine administration of Sandostatin LAR cannot be recommended, particularly in view of its high cost, but more clinical studies should be done especially in somatostatin receptors positive HCC patients.

In general, efficacy of conventional cytotoxic chemotherapy is poor. Although large numbers of controlled and uncontrolled clinical studies have been performed in the last 25 years, no single or combination chemotherapy has been found to be particularly effective.[19,20] All trials of systemic cytotoxic chemotherapies showed low response rates (typically less than 20%) with no survival benefits. This may be in part due to the high rate of expression of drug resistance genes, including p-glycoprotein, glutathione-S-transferase, heat shock proteins, and mutations in p53. Additionally, substantial toxicity limits the use of cytotoxic chemotherapy.

Because of the lack of any survival benefit of treatment with conventional chemotherapy drugs, new agents and novel therapeutic strategies are tried. Growth factors

Keywords: hepatocellular carcinoma, sorafenib, kinase inhibitors, chemotherapy, octreotide

and their corresponding receptors are commonly overexpressed and/or dysregulated in many cancers including HCC. With the arrival of newly developed, molecularly targeted agents and the success of some of these agents in other traditionally challenging cancers, such as renal cell carcinoma, there has been renewed interest in developing novel systemic therapy in HCC. There is a strong rationale for the drug inhibition of molecular components of proliferative and angiogenic components of signaling pathways in HCC. Abnormalities in several cellular signaling pathways have been implicating in HCC tumorigenesis, including receptor activation factor -Raf/mitogen-activated extracellular protein kinase- Mek /extracellular signal regulated-Erk (Raf/Mek/Erk) pathway and angiogenic signaling pathways (like Wnt/β-catenin and PI3K/AKT/mTOR). Erk is the downstream enzyme of the MAP kinase pathway that is directly activated by Raf kinase. The Raf/Mek/Erk pathway is involved in regulating cell proliferation, differentiation, angiogenesis and survival.[21] This pathway is frequently overactivated promoting hepatocarcinogenesis. (Table 1). Additionally, in HCC, a highly vascularised tumor, pro-angiogenic factors such as vascular endothelial growth factor (VEGF) are secreted by tumor cells, endothelial cells and pericytes are essential for the development of new tumor blood vessels, tumor growth, and metastasis[22, 23]. Inhibition of angiogenesis by targeting VEGF and/or the VEGF receptor (VEGFR) represents a potential therapeutic target in HCC.[24,25] (Table 1)

Sorafenib is an oral, anti-angiogenic, pro-apoptotic multi-kinase inhibitor. It targets RAF kinase and tyrosine kinase receptors (mostly VEGFR and platelet derived growth factor receptor-PDGFR) and was found active in hypernephroma therapy. It was shown to have clinical activity in phase I[26] and II HCC trials.[27] A Phase III (Sorafenib HCC Assessment Randomized protocol-SHARP) large (602 cirrhotic well compensated -Child Pugh A status- patients), multicenter, randomized placebo controlled trial evaluated the efficacy and safety of sorafenib (Tab Nexavar® Bayer Pharmaceuticals, tablets of 200 mg, 400mg bid in continuing dosing) versus placebo in patients with advanced HCC (Barcelona Clinic Liver Cancer stage C) with no prior systemic therapy.[28] It should be noticed that 70% of patients had portal vein thrombosis and no locoregional therapy was found effective previously. Primary efficacy endpoints were overall survival and time to symptomatic progression. Secondary points were time to progression and disease control rate. Median

Table 1. Molecular targeted therapy of HCC.

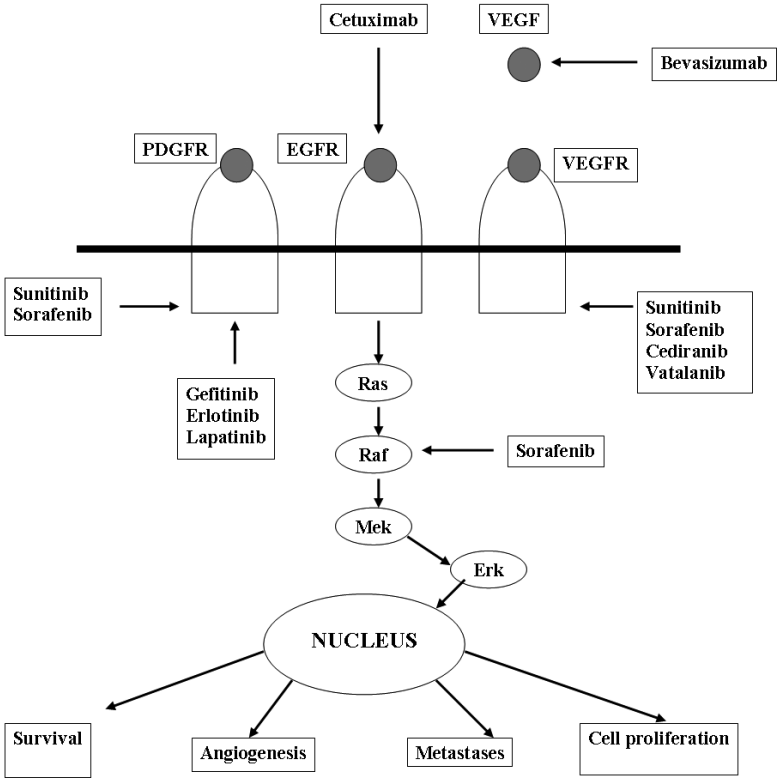
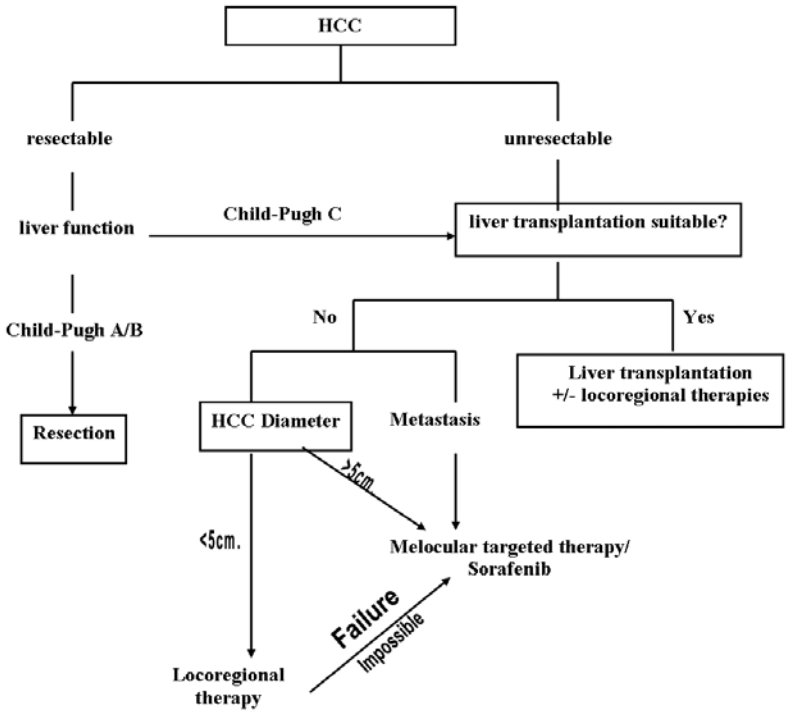


Table 2. HCC therapy.



overall survival was 10,7 months for sorafenib versus 7,9 months for placebo. Based on 321 deaths, the hazard ratio for overall survival was 0,69, representing a 44% improvement in overall survival by sorafenib versus placebo which met early stopping criteria. Median time to progression was longer (5,5 for sorafenib versus 2.8 months for placebo which means a 73% prolongation) and disease control rate was higher (43% versus 32%). In 71% of patients on sorafenib tumor size was found stable and in only 2,3% was reduced. Based on the statistical significance, patients were unblinded and placebo patients were allowed to crossover to sorafenib. Incidence of serious adverse effects was similar for sorafenib versus placebo. The most frequent grade´Y events were diarrhea (11% versus 2% in the placebe group), hand –foot skin reaction (8% versus 1%) fatigue (10% versus 15%) and bleeding (6% versus 9%) for sorafenib versus placebo. These side effects can be managed most of times easily by reducing (halving) the dose of sorafenib. Patients with cancer (mostly hypernephroma) assigned sorafenib have a significant risk of developing hypertension. Appropriate monitoring and treatment is strongly recommended to prevent cardiovascular complications (such as hypertension).[29] Nevertheless, cirrhotic patients are prone to develop systemic hypotension due to portal hypertension and visceral vasodilation and the side effect of hypertension is rare. Sorafenib can be prescribed and the patients followed up by hepatologists-gastroenterolgists with special interest in liver function because of the underlying cirrhosis.

These results have formed the basis for approval of sorafenib for unresectable HCC in the United States and Europe including Greece and established sorafenib monotherapy as the new reference standard systemic treatment for advanced HCC. The combination trial of sorafenib with systemic chemotherapy (doxorubicin) has been completed in Europe and looks promising.[30] For the time being, the safety and benefit of combining molecularly targeted therapy and cytotoxic chemotherapy is not yet established, and it is better not pursuing these strategies outside of the context of a clinical trial[31]. Sorafenib will certainly be assessed in the adjuvant setting after potentially curative resection or ablation and in combination with locoregional treatment modalities (RF and TACE).

After this landmark study, several molecularly targeted therapies, alone or combined with chemotherapy or locoregional attempts, are currently under evaluation for advanced HCC. Targeted therapies under evaluation are agents that inhibit the epidermal growth factor receptor-EGFR, such as the small molecule tyrosine kinase inhibitor gefitinib (Iressa®[30,32,33]), erlotinib (Tarceva®[30,34,35]) and lapatinib[30] and the anti-EGFR chimeric monoclonal

antibody cetuximab (Erbitux®) alone[30] or in combination with chemotherapy.[30] Additionally, other kinase inhibitors (VEGFR, PDGFR) such as Sunitib (Sutent®, active in renal cell carcinoma), Cediranib [30,36] and vatalanib.[30,37,38] are possibly active in HCC.[30] Furthermore, bevasizumab (Avastin®), a monoclonal antibody against VEGF are being studied in HCC treatment as monotherapy[30] or in combination with chemotherapy[30,39] or rapamycin.[40]

In conclusion, the SHARP study represent a breakthrough and has established sorafenib as the new reference standard for the treatment of advanced HCC. (Table 2). All the tested new drugs should be compared to sorafenib. Nevertheless, the side effect profile of each regimen must be carefully considered in patients with advanced liver disease.[41] All anti-HCC drugs should be tested in patients with well preserved hepatic function and good performance status. Patients in well decompensated cirrhotic stage (Child Pugh C) should be given only palliative therapy since the survival can not be changed by any pharmaceutical treatment.

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