Epidemiology
The incidence of hepatocellular carcinoma (HCC) varies worldwide and relates to the incidence of the different aetiologic factors for HCC. Hepatitis B continues to be the most prevalent risk factor, particularly in Southeast Asia and Sub-Saharan Africa [1]. In the western hemisphere, hepatitis C contributes majorly to the continued increase in HCC [2]. In the same region, alcohol contributes to about 25% of the cases [3], while the newly recognized nonalcoholic steatohepatitis (NASH), attributed to morbid obesity [4] and diabetes [5], is partly responsible for the continued rise in HCC [6]. Other risk factors include metabolic disorders, the most common of which is hemochromatosis [7], and environmental factors, the most reported of which are aflatoxins [8], which is responsible for HCC in countries such as Lebanon, and Saudi Arabia [9].

Staging and Scoring
HCC generally develops in the setting of cirrhosis, and thus it is perceived as two problems in one: The cancer itself and the underlying cirrhosis. When assessing patients with HCC, it is important to assess those two aspects. The Child-Pugh scoring system continues to be the classic one used to assess the cirrhosis [10-11], despite its limitation of lacking any parameters pertaining to the cancer per se. Newer scoring systems include factors pertaining to the cancer and include, the Cancer of the Liver Italian Program (CLIP) [12], Chinese University Prognostic Index (CUPI) [13], and Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire Prognostic classification (GETCH) [14].

Systemic Therapy
Treatment options for hepatocellular carcinoma (HCC) depend on the stage of the cancer and the extent of liver cirrhosis. The Barcelona Clinic Liver Cancer [15] staging system provides an algorithm that describes therapeutic options available for each stage of the disease. Despite their curative abilities, only 10% to 15% of patients with HCC are candidates for surgical resection, and 5% meet the criteria for liver transplantation [16]. This stresses that fact that many patients will initially or ultimately require systemic therapy. And of those patients who have undergone potentially curative therapy, the recurrence rate is close to 50% at 2 years [17].

Chemotherapy
Chemotherapy agents have been studied extensively in HCC, and while many clinical trials have showed response rates ranging between 10% and 20%, none have ever demonstrated an improvement in overall survival compared to best supportive care and historical controls. Doxorubicin is the most extensively studied chemotherapy agent in HCC, with a response rate ranging between 2 and 10.5%, based on the three most recent studies [18-20], with no improvement in survival noted. Other chemotherapy agents that have been studied in HCC include [docetaxel] [21], [paclitaxel] [22], [irinotecan] [23], and [gemcitabine] [24], all of which have modest activity. Combination chemotherapy has not fared any better in HCC. A combination of cisplatin, interferon alfa-2, doxorubicin, and 5-fluouracil (PIAF), has shown a response rate of 26% and a median survival of approximately 9 months in a single-
arm phase II trial [25]. Of note is that 13 patients (26%) had a partial response; of these, 9 were considered to have a resectable disease afterwards and underwent surgery and 4 (9%) achieved a complete pathologic response to chemotherapy. These results illustrate that chemotherapy for HCC may be effective in selected patients. These positive results led to the evaluation of PIAF in a large randomized study compared to doxorubicin [20], which however failed to show an improvement in survival (8.6 months for PIAF versus 6.8 months for doxorubicin (p = .83). It is important to note that PIAF regimen was observed to have a high toxicity rate, myelosuppression, fatigue and GI toxicity. Nonetheless these results may support the use of PIAF as a conversion therapy for medically fit patients with good liver function (Child’s A) in whom a response to chemotherapy might permit resection.

Novel Therapeutics
As the basic science efforts have yielded a better understanding of HCC and the relevant pathways involved in carcinogenesis, targeted therapies have begun to be evaluated in parallel in HCC [26].

Two EGFR tyrosine kinase inhibitors have been studied extensively in HCC. Erlotinib was evaluated in a phase II trial of 38 patients with advanced HCC Child-Pugh A [27]. Progression-free-survival at 6 months using Response Evaluation Criteria in Solid Tumors (RECIST) was 32%, with a median progression-free-survival of 3.8 months. There were only 3 partial responses and the median overall survival was 13 months. The most frequent grade 3-4 toxicities were skin rash 13%, diarrhea 8%, and fatigue 8%. Immunohistochemical staining for EFGP expression was not associated with outcome, similar to the findings in other solid tumor malignancies. Lapatinib, a dual inhibitor of EGFR tyrosine kinase 1 and 2 (HER2/Neu), was studied in a phase II trial of 30 patients with advanced HCC [28]. Two of the 17 patients evaluated had a confirmed partial response and 8 had stable disease. The median progression-free-survival was short at 1.8 months. Of note, neither of these two studies evaluated the KRAS status of the patients accrued to the studies, however KRAS mutations are reported to be infrequent in HCC [29-31].

Angiogenesis involving the vascular endothelial growth factor (VEGF) family is a critical target in the development of HCC. Sorafenib, a multi-tyrosine kinase inhibitor, targets angiogenic VEGFR-1, -2, and -3; PDGFR-ß; and tumorogenic RET, Flt-3, and c-Kit receptors, add to serine/threonine kinase Raf-1 [32], has been developed as a therapy for advanced HCC. In a large 137 patients phase II trial evaluating sorafenib in advanced HCC, a low 2% partial response rate was reported [33]. However, 34% of patients had stable disease for at least 4 months commensurate with an independently-reviewed improved median time to progression of 5.5 months. The median overall survival of the study population was 9.2 months, which compares favorably with historical controls. Grade 3 and 4 treatment-related toxicities included fatigue (9.5%), diarrhea (8%), and hand-foot skin reaction (5.1%). For patients who had stable disease, a central tumor necrosis phenomenon was observed on triphasic computed tomography scans (Fig. 1) [33]. The ratio of this tumor necrosis over volume was found later to correlate with objective response [34]. This tumor response parameter is currently being validated prospectively [35].
A large double-blinded, randomized phase III trial (SHARP) evaluated sorafenib compared to placebo in patients with advanced HCC and Child-Pugh A cirrhosis ensued [36]. This trial showed an improvement in survival of 10.7 months in favor of sorafenib versus 7.9 months for placebo (hazard ratio in the sorafenib group, 0.69; 95% confidence interval, 0.55 to 0.87; \( p < 0.001 \)). The drug-related toxicity profile was similar to that noted in the phase II study, with 8% grade 3-4 diarrhea and hand-foot skin reaction, and 4% fatigue. Infrequently, serious grade 3-4 bleeding events (1%) and hypertension (2%), were noted. Based primarily on the results of this trial, and a subsequent randomized phase III study evaluating sorafenib compared with placebo in Southeast Asian countries [37], Government drug oversight agencies worldwide approved sorafenib for patients with unresectable HCC, without any specific reference to the level of liver cirrhosis.

The safety and efficacy of sorafenib in patients with Child-Pugh B or C remain under evaluation. In the phase II study evaluating sorafenib in HCC, 28% of patients had Child-Pugh B cirrhosis [38]. While the pharmacokinetics between the patients with Child-Pugh A and Child-Pugh B were comparable, Child-Pugh B patients had worsening of their liver function more frequently, including increases of serum bilirubin, worsening ascites and encephalopathy. Median time to progression for the Child-Pugh A patients was 21 weeks versus 13 weeks for the Child-Pugh B patients, and the median overall survival were 41 and 14 weeks for the Child-Pugh A and B patients, respectively [39]. While it remains unclear whether this deterioration is drug-related, disease-related, or both, caution is required in applying the results of the SHARP trial to patients with Child-Pugh B or C cirrhosis. Based on a Cancer and Leukemia Group B (CALGB) cooperative group study in which sorafenib was evaluated in 150 patients with multiple degrees of hepatic and renal dysfunction [40], it is recommended that sorafenib be given at the full dose of 400 mg twice daily for patients with a bilirubin level up to 1.5 times the upper limit of normal (x ULN) and 200 mg twice daily (or 400 mg orally daily) for patients with a bilirubin level 1.5-3.0 x ULN. The study was not able to identify a safe dose of sorafenib for bilirubin > 3.0 x ULN.

Several other anti-angiogenic agents have been evaluated in HCC. Bevacizumab...
has been studied extensively in HCC. In a phase II study evaluating bevacizumab as a single agent at 5 mg/kg and 10 mg/kg doses [41], of 46 patients, 6 (13%), achieved an objective response, and 65% of patients were progression-free at 6 months. Median progression-free survival was 6.9 months and median survival time was 12.4 months. Grade 3-5 hemorrhage occurred in 11% of patients, including one death secondary to a variceal bleed. Another study observed similar results [42], in which 3 patients had a partial response and 13 had stable disease among 24 patients who were evaluable.

Sunitinib has been studied in HCC in two different studies and at two doses and schedules of 37.5 mg/day continuous dosing [43], and 50 mg/day in a 4 week-on, 2 off schedule [44]. In the first study, 50% of patients had stable disease, with a median progression-free survival of 3.9 months and overall survival of 9.8 months. The most common grade 3 and 4 adverse events included hematologic toxicities, fatigue, and transaminase elevation. There were two deaths reported on the study attributed to worsening disease and liver failure. In the 50 mg/day study, a low response rate of 2.7% was reported and in addition four deaths were considered possibly drug-related, including associated with hepatic encephalopathy, hematologic toxicities, and a variceal bleed. Regardless, a phase III clinical trial evaluating sunitinib versus sorafenib followed but was terminated early due to higher incidence of serious adverse events in the sunitinib arm compared to the sorafenib arm; additionally sunitinib did not meet the survival study primary endpoint of superiority/non-inferiority of sunitinib compared to sorafenib [45].

Brivanib, a dual inhibitor of VEGF and fibroblast growth factor (FGF) has also been studied in HCC. In a phase II study evaluating brivanib as first- and second-line therapy in 96 patients with advanced HCC, despite limited responses, and a progression-free survival of only 2.7 months in the treatment naïve group, the median overall survival was 10 months in this group [46]. The drug was well tolerated in the second-line setting [47]. A randomized phase III clinical trial comparing brivanib to sorafenib in the front-line setting is currently ongoing [48].

ABT-869, a VEGF and PDGF dual inhibitor, was studied in a phase II study of 44 patients of whom 38 had Child-Pugh A and 6 had Child-Pugh B cirrhosis [49]. The objective response rate for the entire cohort was 6.8%, but all were noted in Child-Pugh A patients. The Child-Pugh A patients had median overall survival of 10.4 months. One fatal adverse event, an intracranial hemorrhage, possibly related to ABT-869 was reported. A large randomized phase III trial of ABT-869 versus sorafenib is currently ongoing [50].

Combination Therapies
Combination therapies including novel therapeutics and chemotherapy have been studied extensively in HCC. These include bevacizumab in combination with gemcitabine and oxaliplatin [51]; bevacizumab in combination with oxaliplatin and capecitabine [52]; and bevacizumab combined with capecitabine [53].

Two studies in particular have yielded interesting results. The combination of bevacizumab and erlotinib was evaluated in patients with HCC, Child-Pugh A or B, and ECOG performance score of 0-2 [54]. The primary endpoint of progression-free survival at 16 weeks was 62.5%, with median progression-free survival of
39 weeks. Median overall survival was 68 weeks and the response rate was 25%. The most common grade 3 and 4 drug-related toxicities were fatigue (20%), hypertension (15%), diarrhea (10%), elevated transaminases (10%), and gastrointestinal hemorrhage (12.5%). The positive outcomes of this study compare favorably with single-agent sorafenib. A randomized phase II study of bevacizumab plus erlotinib and sorafenib is currently under way [55]. A randomized phase III study evaluating sorafenib plus erlotinib versus sorafenib in patients with advanced-stage HCC is also underway [56]. The other promising study is a randomized phase II study of doxorubicin plus sorafenib and doxorubicin plus placebo [18]. The primary endpoint of median time to progression was 9 months for the doxorubicin plus sorafenib arm and 5 months for the doxorubicin plus placebo arm. An exploratory comparison of overall survival between the two arms showed a significant difference of 13.8 months in favor of doxorubicin plus sorafenib versus 6.5 months for doxorubicin plus placebo. Grade 3-4 toxicities included fatigue (15% in both arms) and neutropenia (55% with doxorubicin plus sorafenib and 46% with doxorubicin plus placebo). Sorafenib related toxicities included grade 3-4 diarrhea (11%) and grade 3-4 hand-foot syndrome (9%) in the experimental arm. An increase in mostly asymptomatic left ventricular dysfunction in the doxorubicin and sorafenib arm (all grades: 19%; grade 3-4: 2%) was noted. A large randomized phase III trial evaluating the combination of sorafenib and doxorubicin versus sorafenib is currently underway [35].

Summary
Hepatocellular carcinoma (HCC) is a global health problem. HCC is two diseases in one: underlying liver dysfunction and the cancer itself, both of which require careful management. Scoring systems incorporating both liver dysfunction as well as cancer-related factors are valuable when formulating a treatment strategy. Sorafenib is established as a standard option for patients with advanced-stage HCC [36]. New directions include a combination of antiangiogenic agents with other biologic agents such as bevacizumab and erlotinib [53] or in combination with chemotherapy such as doxorubicin and sorafenib [35]. These approaches appear to be the most promising directions in 2010 and are being tested in large randomized phase III trials. A key point to these improvements is the continued effort in understanding the underlying molecular biology and pathogenesis of HCC.

References


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