Advances in Hepatocellular Carcinoma

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Epidemiology

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, causing 500,000 deaths yearly (1). The continued risk factors that are mostly responsible for the rising incidence of HCC in the Arab world is hepatitis C (HCV). Egypt has the highest prevalence of HCV worldwide (2). Recently calculated weighted mean prevalences of Hepatitis B (HBV) and HCV were 6.7% and 13.9% among healthy populations, and 25.9% and 78.5% among HCC cases in Egypt. Among HCC cases, HBV significantly decreased over time (p=0.001) while HCV did not. Similarly there has been a three-fold increase in the age-adjusted rates for HCC in the western world, up to 7 per 100,000 has been observed (3), and is reportedly explained by the increasing incidence of hepatitis C that has been observed in North America and Europe during in the 80's and early 90's. Another more commonly recognized risk factor is non-alcoholic-steatohepatitis (NASH). NASH related HCC appear to be occur in morbidly obese patients, whose relative risk of death from HCC is 4.52 times higher among men and 1.68 times higher among women, with a body mass index (BMI) ≥ 35, (4). NASH caused HCC is also noted among diabetics who are at increased risk of developing HCC (5).

HCC: Two Diseases in One

In most cases cirrhosis is a direct causative reason and contributes to the morbidity and mortality associated with HCC, thus HCC is essentially two diseases in one. Assessing those two aspects of the disease is imperative. The Child-Pugh scoring system of cirrhosis remains the most commonly used scoring system used by medical oncologists and hepatologists (6-7).

The Child-Pugh score depends on the allocation of 1 to 3 points depending on severity of five parameters: bilirubin, albumin, prothrombin time, clinical ascites, and clinical encephalopathy. Obviously the Child-Pugh scoring system does not account for the stage of cancer, a major limitation that led to the development of many other scoring systems that attempted at evaluating the two aspects of HCC: the cancer itself and the associated cirrhosis.

The Cancer of the Liver Italian Program (CLIP) score was defined and verified prospectively in HCC patients with predominantly a hepatitis C etiology (8). The CLIP includes the Child-Pugh score parameters, plus an assessment of tumor extent in the liver, the presence or absence of portal vein thrombosis, and the level of alpha-fetoprotein (AFP). The Chinese University Prognostic Index (CUPI) scoring system was developed in HCC patients with predominantly a hepatitis B etiology (9). The CUPI parameters are bilirubin, ascites, alpha-fetoprotein, alkaline phosphatase, the tumor extent as defined by the TNM staging system, and the absence or presence of clinical symptoms on presentation.
Other scoring systems include the Groupe d'Etude et de Traitement du Carcinoma Hepatocellulaire (GRETCH) staging system (10), the Okuda staging system (11); the Japan Integrated Staging (JIS) Score (12), which is based on the TNM staging of the Liver Cancer Study Group of Japan (LCSGJ); and the Barcelona Clinic Liver Cancer (BCLC) classification system (13), which was recently validated prospectively (14).

In a retrospective analysis of patients with advanced HCC seen by medical oncologists at Memorial Sloan-Kettering Cancer Center between 2001-2006, we attempted to identify which of these eight scoring systems would be most valuable in this specific clinical setting (15). Using three statistical tools, c-index, the likelihood ratio test and the Akaike Information Criterion, the CLIP scoring systems performed best and this was compatible with the findings of Collete et al. (16). Obviously, this conclusion is limited by the retrospective nature of this analysis and needs to be further validated. On the practical level, using the Child-Pugh scoring system provides most of the information needed for risk-stratifying patients although the CLIP may be more informative in regard to prognosis.

Treatment

There is a continued emergent need for active therapies for advanced HCC considering that most patients present with advanced unresctable or metastatic HCC. In addition 50% of resected patients suffer recurrence within two years and require a systemic therapeutic approach (17). Chemotherapy single agents and in combinations have been tested extensively in HCC. Despite reported responses typical of phase II studies, and ranging between 10-20%, no study has shown an impact on survival (18-21). Given the disappointing results of single-agent therapies, combination regimens have also been investigated. A regimen combining cisplatin, interferon, doxorubicin, and 5-fluorouracil (PIAF) yielded a response rate of 26% and a median survival of 9 months in a recently reported single-arm phase II trial (22). In that study, of the13 patients (26%)

who had a partial response, 9 underwent surgery, and 4 (9%) were found to have had a complete pathologic response to chemotherapy. This study suggests that chemotherapy contrary to the fact, works in some patients with HCC, considering that pathologic complete response was achieved in four cases. This data was also encouraging enough to consider evaluating PIAF as part of a large randomized study which was later performed yet did not show any improvement in survival when compared to single agent doxorubicin (23). And lastly, the data raise the possible use of PIAF in the surgical conversion setting. This approach has already been in use and would be recommended in that specific setting of medically fit patients with good liver function in whom cytoreduction is necessary to permit resectability. These conditions would justify the risk of the high toxicity of the regimen as an acceptable trade-off for potential curability of resectable tumors as part of a multi-disciplinary discussion.

Targeted Therapies in HCC

Other than the discouraging results of chemotherapy and the urgent need for active therapies, studying novel targeted agents seems a reasonable approach considering the presence of several molecular targets involved in the development of HCC. Of those is the Epidermal Growth Factor Receptor (EGFR) whose importance in HCC remains controversial (24-26). The most intriguing results are reported in a phase II study of erlotinib, which showed a 32% 6 months progression-free-survival, with 3 partial responses (8%) and a median overall survival of 13 months (27).

Considering the highly vascular nature of HCC (28-29) anti-agiogenic therapies have been studied extensively in this disease. Sorafenib is a novel molecular targeted agents that inhibits both pro-angiogenic (VEGFR-1, -2, -3; PDGFR-β) and tumorigenic (RET, Flt-3, c-Kit) receptor tyrosine kinases (RTKs). Sorafenib also inhibits the serine/threonine kinase Raf-1 in vitro (30). A phase II trial of sorafenib evaluating response in patients with advanced HCC showed 33.6% of patients had stable disease (≥16 weeks) commensurate with a median time-to-progression (TTP) of 4.2 months and the median overall survival of all patients was 9.2 months (31). Grade 3-4 treatment related toxicities included fatigue (9.5%), diarrhea (8%), and hand-foot skin reaction (5.1%). An interesting observation of central tumor necrosis noted in those patients with stable disease. The ratio of tumor necrosis and volume (N/T) was significantly associated with response, with responders having greater increases in the ratio between necrosis and tumor volume relative to baseline, as compared to non-responders (P=0.02) (32). This phase II study was followed by a large double-blinded, randomized phase III trial evaluating single agent sorafenib versus placebo in patients with advanced HCC and no more than Child-Pugh A cirrhosis (33). This trial demonstrated an improvement in survival of 10.7 months in the sorafenib group versus 7.9 months in the placebo group ($p < 0.001$, HR= 0.69). The drug-related toxicity profile was comprised of 8% grade 3-4 diarrhea and hand foot syndrome. Despite the infrequency of bleeding events (< 1%), one should still use caution in this regard considering the anti-angiogenic nature of sorafenib.

A similar study was performed in Asia-Pacific and showed a statistically significant improvement (p=0.014) in survival was again noted in favor of sorafenib (6.5 month) versus placebo (4.2 months), similar to that noted in the SHARP trial but not to the same magnitude (34). It is worth noting that in the Asian study, patients who were accrued were more ill at start of therapy compared to the SHARP trial. These observations may partly or fully explain the difference in magnitude of benefit from sorafenib between those two populations. The impact of the hepatitis in the Asia-Pacific study pertaining to sorafenib remains un-addressed. Seventy-three per cent of patients accrued on the Asia-Pacific study had hepatitis B as an underlying risk factor, versus 18% of patients on the SHARP trial. From the SHARP trial, it is suggested that patients with hepatitis C may have an added advantage for sorafenib therapy (35). In a sub-group analysis of patients with hepatitis C based HCC, it was noted that these patients treated with sorafenib (n=93) had a median survival advantage of 14 months compared to the whole sorafenib treated group of 10.7 months. In contrast the placebo controlled hepatitis C group did not have any added survival advantage to the placebo population of the study, suggesting a possible positive influence of hepatitis C status on the efficacy of sorafenib. Of note, that the outcome of the 18% of patients with hepatitis B in the SHARP trial, remains to be reported. Similar advantage in favor of patients with hepatitis C and HCC who treated with sorafenib was noted in the phase II study (36).

The exciting results of those two studies apply to patients with preserved performance status and Child- Pugh A score. The safety and efficacy of sorafenib in patients with Child-Pugh B or C cirrhosis needs to be evaluated further. In the phase II study evaluating sorafenib in HCC (37), 28% of patients were Child-Pugh B cirrhosis. In 28 patients from which pharmacokinetic samples were obtained, AUC (0-8)(mg.h/L) was comparable between the Child-Pugh A (25.4) and Child-Pugh B (30.3) patients. Cmax (mg/L) were 4.9 and 6 Child-Pugh A and B patients respectively, with similar drug-related toxicity profiles. However, Child-Pugh B patients had worsening of their liver function more frequently, including transient increases of serum bilirubin, though it is unclear if this deterioration was drug-related or disease progression. Sorafenib acts as a substrate for UGT1A1, and the study did not collect direct bilirubin measurements, so it remains unclear if this total bilirubin elevation is due to worsening liver function caused by sorafenib or simply due to an inhibitory effect of UGT1A1 and decreased bilirubin glucuronidation. The safety of sorafenib in patients with HCC and advanced cirrhosis needs to be further studied. Sorafenib was also evaluated in combination with doxorubicin as part of a randomized double-blinded phase II study of doxorubicin plus sorafenib compared to doxorubicin plus placebo in chemotherapy-naïve HCC patients (38). The primary endpoint, median TTP, 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 13.7 months in favor of doxorubicin plus sorafenib versus 6.5 months for doxorubicin plus placebo (p= 0.0049, HR=0.45). Grade 3-4 toxicities included fatigue (15%), and neutropenia (50%) in both arms. Sorafenib related tocixcity included grade 3-4 diarrhea (11%) and grade 3-4 hand-foot syndrome (9%) in the combination arm. There was more left ventricular dysfunction in the doxorubicin plus sorafenib arm, having been reported in 19% of the cases (all grades) with 2% grade 3-4. A potential synergistic effect between doxorubicin and sorafenib leading to worsening cardiac function may exist and needs to be further elucidated. A larger randomized trial evaluating the combination versus sorafenib alone is underway.

Bevacizumab has been studied extensively in HCC, as a single agent (39-40), in combination with chemotherapy (41-43) and biologics (44). The most promising bevacizumab doublet data is in combination with erlotinib (44). Patients with HCC and CLIP ≥ 3 were treated with bevacizumab and erlotinib. Based on an intent-to-treat analysis, 10 of 40 patients had radiographic responses The median PFS was 9 months, and the median overall survival was 15.6 months. Grade 3 and 4 fatigue and hypertension were each reported in 20 and 15% of the cases respectively. Similar grade gastrointestinal bleeds were reported in 12.5% of the cases. While these represent only pilot results and may reflect a select group of patients, the outcome of this study supports the biologic relevance of this combination of anti-angiogenic therapy and tyrosine kinase inhibitor in HCC.

Sunitinib, a multi-targeted tyrosine kinase inhibitor, has also been tested in HCC

(45). Of 26 patients treated with sunitinib at 37.5 mg daily dose, 10 (38.5%) showed stability of disease, with a median PFS of 4.1 months. In this particular study. Another study showed similarly promising results at the dose of 50 mg, with median TTP of 21 weeks and median OS of 45 weeks (46). Sunitinib is currently studied against sorafenib in a randomized phase III study (47).

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