Response to sorafenib therapy in hepatocellular carcinoma of viral vs. alcoholic etiology: a retrospective analysis

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1. Study Purpose and Rationale

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, with approximately 600,000 new cases diagnosed each year, and it represents the third leading cause of cancer deaths worldwide [1]. The development of HCC is a multistep process, beginning in nearly all cases with chronic liver disease or cirrhosis, and progressing through dysplastic nodule formation to invasive cancer [2]. Underlying liver disease that predisposes to HCC can be a result of diverse factors, including viral hepatitis, alcohol use, or exposure to toxins such as aflatoxin B. A common theme among these diverse causes is the sustained cycle of liver injury and necrosis, followed by inflammation and regeneration of hepatocytes. This chronic injury cycle is a key element in hepatocellular carcinogenesis, both through the propagation of oncogenic changes and the induction of liver fibrosis, which creates a permissive microenvironment for HCC [3].

The burden of disease of HCC is significantly greater in sub-Saharan Africa and Eastern Asia, areas where viral Hepatitis B is endemic. Incidence of HCC in the United States is increasing sharply, having tripled in the last 20 years. HCC caused by Hepatitis C virus is currently one of the fastest-growing causes of tumor-related death in the US [4], in addition to increases in rates of non-alcoholic fatty liver disease (NAFLD).

The long-term prognosis for this cancer remains quite poor, with less than 12% of patients surviving 5 years from diagnosis [4]. Poor clinical outcomes are thought to be a result of several factors. Disease is often very advanced at the time of diagnosis, with few patients eligible for curative surgical resection or liver transplantation. Patients also tend to have little hepatic reserve function due to underlying liver disease. Lastly, traditional chemotherapy with systemic cytotoxic agents has little, if any, proven benefit – no traditional chemotherapeutic regimen has been shown to improve survival in HCC [5, 6]. Thus, there is an urgent need for advancements in both diagnosis and therapy.

The approval in 2007 of sorafenib, a multikinase inhibitor, for advanced HCC was a major breakthrough in the treatment of this aggressive cancer. Sorafenib counteracts the proliferative effects of the MAP kinase pathway by inhibiting the serine-threonine kinase activity of Raf, in addition to anti-angiogenic effects through inhibition of the tyrosine kinase activity of vascular endothelial growth factor (VEGF) receptors. Both of these pathways are hypothesized to be important in the pathogenesis of HCC [7].

Sorafenib was approved in the United States for the treatment of unresectable HCC as a result of two large-scale studies. The first, the SHARP trial (Sorafenib HCC Assessment Randomized Protocol), consisted of 602 patients, from a primarily European population, that were randomized to sorafenib, 400 mg twice daily, or placebo. The sorafenib group had a median survival of 10.7 months, whereas the placebo group had a median survival of 7.9 months

($p<0.001$) [8]. A second study, with a population of 271 patients from Asia, where Hepatitis B is endemic, found a median survival of 6.5 months for sorafenib vs. 4.2 months for placebo ($p=0.014$) [9]. As a result of these two studies, sorafenib was approved for this indication by the FDA, and has since become very common for the treatment of advanced HCC.

A remaining question with regard to sorafenib's efficacy is whether the response to treatment differs based on the underlying etiologic factor of a patient's cancer – specifically, whether patients with underlying Hepatitis B or C respond differently than patients with cirrhosis of a primarily alcoholic etiology, for example. A post-hoc subgroup analysis of the SHARP trial suggested that response may be more favorable in patients with Hepatitis C compared to those with Hepatitis B or alcoholic cirrhosis [10], but the original study was not powered for these subgroup analyses. Further investigations are needed to better understand this issue, potentially helping to better target the use of sorafenib among subpopulations of patients with HCC.

Interestingly, it has been proposed that sorafenib may have better activity against HCC in the setting of underlying Hepatitis C for two reasons. First, Hepatitis C is known to cause dysregulation in the MAP kinase pathway, which is one of the targets for inhibition by sorafenib [11]. Second, it has been proposed that sorafenib may, in fact, have direct anti-viral activity against Hepatitis C based on studies in model systems [12]. While these proposals require further evaluation, they are intriguing with regard to sorafenib's efficacy in this disease setting.

Here, we hypothesize that patients with hepatocellular carcinoma secondary to Hepatitis C-induced cirrhosis will have a better response to sorafenib monotherapy than patients with disease secondary to alcohol-induced cirrhosis, as assessed by median survival and time to progression. This hypothesis will be evaluated through a retrospective analysis of HCC patients treated at this center since the approval of sorafenib in 2007.

2. Study Design and Statistical Procedure

This study will consist of a retrospective analysis of data from patients with advanced HCC that underwent treatment with sorafenib at New York Presbyterian Hospital between 2008 and 2012. Advanced HCC will be defined as disease that was deemed to be unresectable based on imaging, or disease that recurred after initial surgical resection. These patients will be identified through billing records, and a chart review will then be conducted to assess information such as age, sex, viral hepatitis serologies, alcohol history, size of tumor at the start of therapy based on imaging, duration of sorafenib therapy, and results on follow-up imaging. Patients will be divided into two groups: those with positive serologies for Hepatitis C, and those

Sample size / power analysis: In order to power the study, it was estimated that overall survival at nine months would be comparable to that observed in a prior subgroup analysis, which found median survival of 14.0 months in HCV-induced HCC patients treated with sorafenib and 10.3 months in alcohol-induced HCC treated with sorafenib [10]. Based on these findings, we estimated that survival at 9 months after initiation of therapy would be approximately 50% in the alcohol-induced group, and 75% in the HCV-induced group. A conservative estimate for standard deviation of 3 months was used. Therefore, in order to achieve a level of $\alpha=0.05$ and a power of 0.80:

Using t-test comparing median survival:
Sample size = 12 patients in each group

Using chi-square test comparing % survival at 9 months:
Sample size = 65 patients in each group

Based on the larger sample size estimate, we will plan to include 150 patients total in this analysis.

Study data will be analyzed by creating Kaplan-Meier survival curves for the two different populations among the larger HCC cohort. Through this analysis, median survival and time to progression while on sorafenib for each group will be calculated. Progression of disease will be defined according to RECIST criteria for progression of solid tumors, which are based on well-characterized findings on imaging. Differences in median survival and time to progression will then be assessed for statistical significance using log-rank tests, as described previously.

3. Study Procedures

No procedures will be conducted during this retrospective data analysis.

4. Study Drugs or Devices

Sorafenib is a multi-kinase inhibitor, dosed in an oral formulation, with activity against several intracellular signaling pathways. It is currently approved in the United States for the treatment of patients with unresectable HCC. Sorafenib is generally well-tolerated in a broad population of patients - observed toxicities include hand-foot syndrome, diarrhea, fatigue, and rash.

Of note, no new drugs will be administered to patients in this retrospective analysis.

5. Study Subjects

Patients to be included in this analysis will be those treated at NYP for advanced HCC, as defined by the below criteria, between 2008 and 2012, who received sorafenib monotherapy for a minimum duration of 3 continuous months. For the purpose of this preliminary analysis, we will exclude patients with HCC that is presumed secondary to Hepatitis B infection, as this etiology is less common in our study population, and these tumors may behave more aggressively compared to those secondary to other etiologic factors, based on previous studies [10]. We will also plan to exclude patients with extrahepatic metastatic disease at the time of initiation of treatment.

Inclusion criteria:

- >18 years of age
- Definitive diagnosis of hepatocellular carcinoma based on imaging or pathology
- Presence of advanced disease, as defined by extensive intrahepatic spread, unresectability, or recurrence after prior surgical resection
- Treated with sorafenib for at least 3 months continuously

Exclusion criteria:

- Positive serology for Hepatitis B infection
- Extrahepatic spread of disease at the time of initiation of treatment
- Simultaneous treatment with additional chemotherapeutic agents
- Discontinuation of sorafenib therapy earlier than 3 months

6. Recruitment of Subjects

There will be no active recruitment of new patients for this study. Patients will be identified through review of charts and billing records, as detailed above, and they will have already consented to use of their health information for research purposes.

7. Confidentiality of Study Data

Collection of patient data will be limited to only the amount necessary to achieve the goals of the study, in order to prevent collection of unneeded sensitive data. All study data will be kept only on password-protected and/or encrypted computers or hardware. Wherever possible, patient data will be de-identified to further protect sensitive patient information.

8. Potential Conflict of Interest

No potential conflicts of interest are identified.

9. Potential Risks

The only potential risks of this study are disclosure of patient's protected health information, and precautions will be taken, as detailed above, to minimize this risk.

10. Potential Benefits

The potential benefits of this study include achieving a better understanding of the response to sorafenib among different populations of patients with HCC. This could help to better target sorafenib therapy to patients who are most likely to benefit, thus maximizing its therapeutic efficacy while limiting toxicity among patients that are unlikely to benefit from its use.

11. Alternative Therapies

Not applicable

12. Compensation to Subjects

Since this is a retrospective analysis, no compensation to subjects will be provided.

13. Costs to Subjects

Since this is a retrospective analysis, there will be no costs incurred by the subjects.

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