

Effects of Sorafenib vs. Sorafenib plus Metformin on survival in advanced Hepatocellular Carcinoma

A double-blinded, randomized control trial

A. Study Purpose and Rationale

Hepatocellular carcinoma (HCC) is a common cancer that has the third highest cancer-related mortality rate worldwide. The disease is potentially curable by transplantation if detected early, however, the majority of cases are diagnosed at an advanced stage for which limited treatment options are available.¹ A study published in the *New England Journal of Medicine* in 2008 convincingly demonstrated that Sorafenib, a multikinase inhibitor of vascular endothelial growth factor, platelet-derived growth factor receptor, and Raf, improved median survival by approximately three months in patients with advanced hepatocellular carcinoma. Patients were classified as having advanced disease if they were not eligible for or had disease progression after surgical or locoregional therapies. The impact of this study was significant since no consistent survival benefits for anticancer agents in hepatocellular carcinoma have been recorded in approximately 100 randomized studies reported during the past 30 years. However, even with Sorafenib in advanced HCC, prognosis remains poor. In recent years, many molecularly targeted agents that inhibit different pathways of hepatocarcinogenesis are under various phases of clinical development and novel targets are being assessed.⁷ Of these targets, both mTOR and VEGF receptor are currently undergoing evaluation as second-line therapy for HCC in clinical studies. Specifically, the biologic rationale for the role of mTOR in the pathogenesis of HCC is supported by several pre-clinical studies. In human HCC cell lines, Everolimus, Sirolimus, and Temsirolimus have been shown to inhibit cell growth and proliferation.³ Even in mouse models, Everolimus and Sirolimus significantly reduced tumor volume, angiogenesis, delayed tumor growth, and increased overall survival compared with controls.³ Clinical studies are ongoing that are evaluation combination therapy with Sorafenib and mTOR inhibitors.⁴ However, mTOR inhibitors are still very experimental agents with high costs and a robust adverse effect profile (fatigue, skin rash, stomatitis, hematologic abnormalities). Metformin, via the activation of the LKB1-AMPK pathway, can reduce the activity of mTOR which can lead to anti-tumorigenesis effects. Metformin is an inexpensive medication with a safe, well-studied adverse effect profile that can be easily administered in combination with Sorafenib, the new standard of care in patients with advanced hepatocellular carcinoma.

B. Study Design and Statistical Analysis

The study, a double-blinded randomized control trial, will compare the differences in median survival in patients with advanced HCC who take Sorafenib 400 mg twice daily plus Placebo vs. patients who take a combination of Sorafenib 400 mg twice daily plus Metformin 750 mg twice daily. The study length will be one year.

The study population will consist of patients with advanced hepatocellular carcinoma (HCC) defined as having disease progression after surgical or locoregional therapies OR were not eligible for surgical interventions due to extent of disease. Other inclusion criteria are: ECOG performance status of 2 or less (at a minimum, being up and about equal to or greater than 50% of waking hours), Child-Pugh liver function class A (based on total bilirubin, serum albumin, PT/INR, ascites, hepatic encephalopathy), life expectancy of 12 weeks or more, adequate hematologic function (platelet count $\geq 60,000/\mu\text{L}$, hemoglobin ≥ 8.5 g/dL, INR ≤ 2.3 , or PT ≤ 6 seconds above control), adequate hepatic function (albumin ≤ 2.8 g/dL, total bilirubin ≤ 3 , ALT an AST ≤ 5 time the upper limit of normal), adequate renal function (serum Cr, ≤ 2.0). Patients will be excluded if they have received previous molecular targeted therapies or any other systemic treatment, however, concomitant anti-viral systemic therapy will be allowed.

Patients will be randomized into either the Sorafenib/Placebo or Sorafenib/Metformin arm via blocked randomization in order to create adequate equality in the number of patients in each arm. Assuming a type I error rate of 0.05, and a randomization ratio of 1:1 between the two groups, and an expected 20% improvement in median survival in the Sorafenib/Metformin group, a total of 80 subjects will need to be enrolled in order to have 80% power. There will be no crossover allowed from one arm to another.

At the end of the study survival curves will be generated via Kaplan-Meier analysis and to determine if a statistical difference exists in median survival, a logrank test or Chi squared test will be performed. If there are no censored data (unlikely), the Wilcoxon sum of ranks test can be used.⁸

C. Study Procedure

Once the patients are randomized into respective groups treatment will begin. The Sorafenib arm will receive 400 mg po twice daily and the Sorafenib plus Metformin group will receive the same daily dose of Sorafenib plus a total of 750 mg of Metformin twice daily. Compliance will be assessed on the basis of pill counts. Safety assessments will include documentation of adverse events, clinical laboratory tests, physical examination, and measurement of vital signs. The patients will be assessed every 4 weeks during the study. Also, a weekly phone call by a study nurse will take place to check-in on patients and minimize the chances of participant drop-out or loss to follow-up.

D. Study Drugs

Sorafenib: This drug is an oral Multi-kinase inhibitor administered on an empty stomach that inhibits tumor growth and angiogenesis by inhibiting intracellular Raf kinases (CRAF, BRAF, and mutant BRAF), and cell surface kinase receptors (VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-beta, cKIT, FLT-3, and RET). The medication is approved by the FDA for the treatment of advanced Hepatocellular Carcinoma.² Sorafenib was shown to improve median overall survival in advanced HCC (10.7 months compared to 7.9 months with placebo)². Also, survival rates at 1 year were 44% in the Sorafenib group compared to 33% in the placebo group corresponding to a 31% relative reduction in the risk of death. The most common adverse reactions reported are (>10%): hypertension, fatigue, sensory neuropathy, rash/desquamation, hand-foot syndrome, pruritis, hypoalbuminemia, hypophosphatemia, hypocalcemia, diarrhea, nausea/vomiting, elevated amylase/lipase, abdominal pain, anorexia, lymphopenia, thrombocytopenia, neutropenia, liver dysfunction, dyspnea, and cough. Metabolism of Sorafenib occurs primarily in the liver and is mediated via cytochrome P450 (CYP) 3A4 and uridine diphosphate glucuronosyltransferase 1A9.

Metformin: This drug is approved for the treatment of Type 2 Diabetes Mellitus. It is efficacious in this disease improving insulin sensitivity, decreasing hepatic gluconeogenesis, and decreasing glycogenolysis with the result of lower fasting blood glucose levels. This medication is not approved for the treatment of Hepatocellular Carcinoma. The rationale for its use in this study stems from the established knowledge that Metformin can suppress tumorigenesis via the LKB1-AMPK pathway. Cell-cycle arrest in response to Metformin requires CDK inhibitors, P21, and p27 in addition to Cyclin D1 down regulation and AMPK activation in breast cancer cell lines.⁵ Recently, the dose-dependent chemopreventive effect of metformin was confirmed in hepatoma cell lines. Metformin was demonstrated to inhibit cell growth through cell cycle G0/G1 arrest via reduction in Cyclin D1 expression, increases in AMPK phosphorylation, P21 and P27 expression. AMPK is a central cellular energy sensor whose activation leads to suppression of many of the processes highly dependent on ample cellular ATP supply. Metformin directly inhibits complex 1 of the respiratory chain leading to decreased ATP synthesis and a rise in the cellular AMP:ATP ratio, mimicking conditions of cellular energy stress. Increased association of AMPK with AMP under such conditions facilitates its phosphorylation and activation by the upstream kinase LKB1. Activation of AMPK results in phosphorylation and stabilization of the protein product of the TSC2 tumor suppressor. TSC2 negatively regulates a small GTPase Rheb which serves as a binary switch for the

most regulator of eukaryotic protein synthesis mTOR. When activated, mTOR has a strongly positive effect on protein translation and cellular proliferation. Though Metformin has not been used specifically in randomized clinical trials for the treatment of HCC, its long history of use for the treatment of Type 2 Diabetes has let us examine its short-term and long-term safety profile. The most common adverse effect of Metformin is GI irritation (~50%) including diarrhea, cramping, nausea, vomiting, and increased flatulence. The most potential serious side effect of Metformin use is lactic acidosis.⁶ This complication is very rare, and the vast majority of these cases seem to be related to comorbid conditions such as severely impaired Liver or Kidney function rather than to Metformin itself. The dose in the study will be 750 mg by mouth twice daily which is below the maximum dose of 2550 mg/day. Metformin is not metabolized but instead excreted unchanged in the urine with a half-life of approximately 5 hours.

E. Medical Devices

N/A

F. Study Questionnaires

N/A

G. Study Subjects

The study population will consist of patients with advanced hepatocellular carcinoma (HCC) defined as having disease progression after surgical or locoregional therapies OR were not eligible for surgical interventions due to extent of disease. Other inclusion criteria are: ECOG performance status of 2 or less (which translates to at a minimum, being up and about equal to or greater than 50% of waking hours), Child-Pugh liver function class A (based on total bilirubin, serum albumin, PT/INR, ascites, hepatic encephalopathy), life expectancy of 12 weeks or more, adequate hematologic function (platelet count \geq 60,000/uL, hemoglobin \geq 8.5 g/dL, INR \leq 2.3, or PT \leq 6 seconds above control, adequate hepatic function (albumin \leq 2.8 g/dL, total bilirubin \leq 3, ALT an AST \leq 5 time the upper limit of normal), adequate renal function (serum Cr, \leq 1.5). Patients will be excluded if they have received previous molecular targeted therapies or any other systemic treatment, however, concomitant anti-viral systemic therapy will be allowed. This study will be open to all men and women who meet the inclusion criteria regardless of race/ethnicity.

H. Recruitment of Subjects

The Liver Cancer Database at the Herbert Irving Comprehensive Cancer Center will be utilized to identify potential candidates for the study. A phone call will be made to each individual patient with a standardized script that explains the purpose of the phone call, the reason for the study, study design, length, outcome measures, and an explanation of the adverse effects of all study medications. If the patient agrees to participate, more detailed information will be mailed to them with a study e-mail address, return address, and phone number provided for further correspondence.

Prior to randomization, we will contact the patient's PMD for agreement that the patient is suitable for the study.

I. Confidentiality of Study Data

To ensure patient privacy, the patient's information will be coded with a unique identification code that is 7 digits in length that will not include any part of his or her social security number, phone number, address, or hospital medical record number. These codes will be generated by a computer.

J. Potential Conflict of Interest

It is not anticipated that any of the investigators will have a proprietary interest in any of the study drugs or will stand to benefit financially in any way from the results of the investigation.

K. Location of the Study

The medications will be self-administered by the patients in their own residence. For the monthly follow-up visits, patients will be evaluated in a clinical area of CUMC.

L. Potential Risks

The potential risks and discomforts of the study are related to the potential adverse effects of the medications taken as outlined above. The participants will be informed of these specific adverse effects before randomization occurs. The participants will also be made aware before randomization that there is a 50% chance that they will be taking Placebo instead of Metformin. All participants will be made aware that the study medications will be provided at no cost to them.

M. Potential Benefits

A statement of potential benefits will be made explicitly available to the participants. Potential benefits include: a longer survival time than if not enrolled in the study, study medication is free of charge (Sorafenib out of pocket can cost \$5000 a month). Also, the patient's will be made aware about the significant contribution they are making to society by participating in a study attempting to advance therapy for the treatment of HCC.

N. Alternative Therapies

There are not many alternative therapies available for patients with advanced HCC. Systemic chemotherapy with Doxorubicin has been used, but has not shown to increase survival. Sorafenib alone is approved for the treatment of advanced HCC. Other clinical trials are ongoing that include a combination of Sorafenib with other molecularly targeted therapies.

O. Compensation to Subjects

No compensation will be provided for participation in this study.

P. Costs to Subjects

The participants will not incur any costs as a result of participating in the study.

Q. Minors as Research Subjects

No minors will be involved in this study.

R. Radiation or Radioactive Substances

No radiation will be used in the study.

References

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