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CRC Course
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Research Question: Does the response of metastatic hepatocellular carcinoma to the chemotherapeutic agent sorafenib vary in relationship to serum leptin levels?

1. Study Purpose and Rationale

Hepatocellular carcinoma is a malignancy of global significance, as it is the sixth most common cancer and third most common cause of cancer-related mortality worldwide. Historically, HCC has had a higher incidence in Asia due to the prevalence of hepatitis viruses in the population; however, the incidence of HCC has been notably increasing in United States and Europe over the past 35 years.

Recurrence rates of HCC vary after surgical resection, and most notably in relationship to the Milan criteria, which shows a recurrence rate of approximately 42% for lesions >5cm or for patients with more than three lesions, and a recurrence rate of 5-8% for lesions that do not meet this criteria. For patients with evidence of vascular invasion or extra-hepatic spread, the survival rates at 1, 2, and 3 years are 29%, 16%, and 8% respectively. The importance of developing effective systemic therapy in HCC is thus of great interest given the dismal prognosis of the disease.

Sorafenib is a chemotherapeutic agent licensed in 2007 for use in patients with advanced HCC for whom locoregional intervention and surgery are unsuitable or have been unsuccessful. The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) showed that sorafenib, on average, improves overall survival by 83 days relative to placebo--a 44% increase in survival time from 7.9 months to 10.7 months.

Sorafenib, an agent that inhibits angiogenic growth factor receptors, ushered in an era of of molecular-targeted therapy in HCC, as its demonstration of improved survival was a breakthrough in treatment for those with advanced disease. Its success has also emphasized the importance of research into the role of angiogenic growth factor receptors in the pathogenesis and progression of HCC.

One such factor that has been found to increase angiogenesis and growth factor expression in HCC is the peptide hormone leptin. Leptin, a circulating hormone directly associated with high BMI, can act as a mitogen and angiogenic factor. Furthermore, leptin has been found to have a direct stimulator effect on HCC cell migration and invasion. The therapeutic implications of leptin's role in carcinogenesis have yet to be elucidated.

The question is thus whether there is a relationship between response to an agent such as sorafenib that inhibits angiogenic growth factor receptors and increased expression of these receptors due to higher circulating levels of leptin. Additionally, the question arises whether this relationship has implications for treatment by suggesting that patients treated with sorafenib who have increased leptin levels will have greater response, and therefore longer survival time, than counterparts with lower serum leptin levels.

2. Study Design and Statistical Procedures

This study will be designed as a retrospective study using the data from SHARP, a multicenter, phase 3, double-blind, placebo-controlled trial. Patients with advanced hepatocellular carcinoma received either sorafenib or placebo.

The data from this study will be analyzed with a Cox proportional hazards model. The covariates will be 1.) Leptin measured as a continuous variable and 2.) The interaction term of leptin + sorafenib treatment. This analysis will relate recurrence rate to leptin levels, and indicate if there is a significant interaction leading to effect difference of leptin in drug versus placebo group.

3. Study Procedures

Leptin levels will be measured from serum samples using a monoclonal antibody directed towards the peptide hormone and detected by sandwich type fluorescence immunoassay. Monoclonal antibodies interact with a single defined epitope, allowing for precise and reliable measurement, and will be less affected by degradation products from stored samples. Similarly, a sandwich assay will be used as it is less susceptible to bias caused by circulating analyte fragments. Parallel measurement of free and circulating leptin will be obtained and summed for a total circulating leptin level.

The leptin specimens should be stored frozen at –80°C. Hemolyzed or lipemic samples should not be analyzed. The frozen samples should be equilibrated to room temperature (RT) before analysis, then mixed thoroughly by gentle inversion or vortexing prior to use.

Materials required include a commercially available ELISA Antibody kit, polystyrene test tubes/96-well microtiter plates, test tube racks, precision and repeating pipets, sponge rack for decantation, or a vacuum suction device, centrifuge/microcentrifuge, microtiter plate shaker. The assay procedure takes approximately 6 hours.

Software for calculating the final results should be installed on the detection system and analyzed with a log-linear curve fit.

4. Study Drugs

Sorafenib is a multikinase inhibitor with activity against Raf kinase and multiple tyrosine receptor tyrosine kinases, including vascular endothelial growth factor receptor, (VEGFR2), platelet-derived growth factor receptor (PDGFR), FLT3, ret, and c-Kit.

The drug is approved for treatment of patients with renal cell carcinoma as well as for patients with advanced HCC. It is an oral formulation. The recommended daily dose 400 mg (2 x 200 mg tablets) taken twice daily without food (at least 1 hour before or 2 hours after a meal).

The most common adverse reactions reported for sorafenib-treated patients vs. placebo-treated patients in unresectable HCC, respectively, were: diarrhea (55% vs. 25%), fatigue (46% vs. 45%), abdominal pain (31% vs. 26%), weight loss (30% vs. 10%), anorexia (29% vs. 18%), nausea (24% vs. 20%), and hand-foot skin reaction (21% vs. 3%). Grade 3/4 adverse reactions were 45% vs. 32%.

The method, route of administration, and dosage regimen are consistent with standard therapy.

5. Study Questionnaires

N/A

6. Study Subjects

The patients will be those included in the SHARP. These patients had hepatocellular carcinoma proven by histology, evidence of advanced disease by imaging (macroscopic vascular invasion or extra-hepatic spread), no prior systemic treatment, and ECOG Performance Status 0-2 and Child-Pugh status of A, life expectancy of 12 weeks or more.

Additional inclusion criteria included: adequate hematologic function (platelet count, ≥60×109 per liter; hemoglobin, ≥8.5 g per deciliter; and prothrombin time international normalized ratio, ≤2.3; or prothrombin time, ≤6 seconds above control), adequate hepatic function (albumin,≥2.8 g per deciliter; total bilirubin, ≤3 mg per deciliter [51.3 μmol per liter]; and alanine aminotransferase and aspartate aminotransferase, ≤5 times the upper limit of the normal range), and adequate renal function (serum creatinine, ≤1.5 times the upper limit of the normal range).

Serum leptin values will be taken from all intact samples that have been stored at the appropriate temperature without hemolyzation. No adjustments will be made in this study for time of day of leptin measurement or for time since last meal as this data may not be consistently available.

7. Recruitment

N/A

8. Confidentiality of Study Data

The confidentiality will be consistent with the prior study, for which all patients signed informed consent. All study participants will be coded with a unique code used for analysis of serum leptin levels. Data will be stored on a secure electronic storage device, password protected and only accessible to investigators.

9. Potential Risks

As this is a retrospective study, there are no new risks to participants in the previous studies.

10. Potential Benefits

In regards to the population of study, that is patients with advanced HCC, the data regarding who will respond well to chemotherapeutic agents could have potential benefit to guide decisions for therapy. By knowing the likelihood of response to therapy, patients could be stratified as to those to treat aggressively versus patients for whom the potential benefits may not outweigh the side effects of treatment or that another treatment modality may be more beneficial.

The data may have greater implications for adjuvant chemotherapy treatment options in post-transplant patients. Currently, the recurrence rate for HCC in patients receiving a liver transplant, who are by definition patients without evidence of metastasis, is quite variable but approximately 18%. The Milan criteria are currently used to stratify patients as to likelihood of recurrence, however, there is data that suggests these criteria may be too stringent and alternate methods of stratification or treatment protocols may be warranted.

If patients can be assessed for responsiveness to a chemotherapeutic agent and this data could be used to predict success of not only prolonging survival time but preventing recurrence, this would allow for improved post-transplant treatment plans. That is, patients with high leptin levels and VEGF expression could be given adjuvant chemotherapy as a prophylactic measure to prevent recurrence. The data could also be used to improve organ utilization and outcomes by allowing patients with more advanced HCC but with favorable tumor biology and/or serum markers to be offered transplantation coupled with adjuvant chemotherapy.

11. Alternatives

-Treat all patients with sorafenib regardless of leptin levels or tumor biology as is the approved use of the agent.
- Treat no patients with sorafenib after liver transplantation until recurrence, as is the current model.

References

Altekruse, Sean, K. McGlynn, and M. Reichmann. Liver Cancer Rates Triple: Hepatocellular Carcinoma Incidence, Mortality, and Survival Trends in the United States from 1975 to 2005. Journal of Clinical Oncology (2009) 27: 1485-1491

Bidlingmaier, Martin and Matthias Tschoep. Immunoassay Measurements of Leptin. Methods in Molecular Biology, vol. 155: Adipose Tissue Protocols. Edited by: G. Ailhaud © Humana Press Inc., Totowa, NJ

De Vera, Michael E. Getting a Handle on Posttransplant Recurrence of HCC. ONCOLOGY 2009. Vol. 23 No. 14

Kaseb, A.O. et al. A 10 year retrospective analysis of risk factors, patterns of cancer recurrence, and survival after liver transplant for cirrhosis and hepatocellular carcinoma. Journal of Clinical Oncology (2007) 25: 4617.

Llovet JM, Burroughs A, Bruix J. Hepatocellular Carcinoma. Lancet 2003 Dec 6;362(9399):1907-17.

Llovet, Joseph at al. Sorafenib in Advanced Hepatocellular Carcinoma. NEJM 2008 359;4

Saab S, McTigue M, Finn RS, Busuttil RW. Sorafenib As Adjuvant Therapy For High-Risk Hepatocellular Carcinoma in Liver Transplant Recipients: Feasibility and Efficacy. Exp Clin Transplant Dec 2010 2010 Dec;8(4):307-313.

Sharma, D., Wang, J., Fu, P. P., Sharma, S., Nagalingam, A., Mells, J., Handy, J., Page, A. J., Cohen, C., Anania, F. A. and Saxena, N. K. (2010), Adiponectin antagonizes the oncogenic actions of leptin in hepatocellular carcinogenesis. Hepatology, 52: 1713–1722. doi: 10.1002/hep.23892

Stefanou N, Papanikolaou V, Furukawa Y, Nakamura Y, Tsezou A. Leptin as a critical regulator of hepatocellular carcinoma development through modulation of human telomerase reverse transcriptase. BMC Cancer. 2010 Aug 19;10:442.

Wang, S-N. Potential role of leptin expression in hepatocellular carcinoma. J Clin Pathology (2006) 59: 930-934.

Zhang L, Ren ZG, Gan YH, Wang YH, Zhang BH, Chen Y, Xie XY, Ge NL, Ye SL. Therapeutic efficacy and prognostic factors of sorafenib treatment in patients with unresectable primary hepatocellular carcinoma. Liver Cancer Institute, 2010 Aug;32(8):630-3.

Zhu, Andrew X. Systemic Treatment of Hepatocellular Carcinoma:Dawn of a New Era? Ann Surg Oncol (2010) 17:1247–1256