Does CP461 Decrease Tumor Burden in HCC Patients Awaiting Liver Transplant?

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A. Study Purpose and Rationale

Hepatocellular carcinoma (HCC) is one of the most common tumors worldwide, resulting in up to 1 million deaths each year. It is associated with cirrhosis in 80% of cases and is most prevalent in areas of high HBV and HCV infection, including sub-Saharan Africa and Southeast Asia. However, the incidence of HCC has been rising in the US in recent years.

Historically, the prognosis of HCC has been dismal, with mean survival after diagnosis of between six and twenty months. This observation has been attributed to several factors, including advanced stage at diagnosis and rapid clinical deterioration. HCC is notoriously resistant to chemotherapeutic regimens: a recent review of 37 RCTs found that no agent was efficacious in prolonging survival and concluded that the use of chemotherapy was not justified in these patients [1]. Other agents such as tamoxifen and interferon have shown only limited efficacy in a few studies [2i]. Local therapies include percutaneous alcohol injection (PEI), radiofrequency ablation, and transarterial chemoembolization. While these therapies can be curative in the minority of patients diagnosed with limited disease, they are more frequently used as palliative treatment in patients with more advanced disease. Other potentially curative therapies include surgical resection, again available to only a minority of patients presenting with small HCCs, and liver transplantation. [3]

Liver transplantation is a potentially curative therapy that has been shown to improve mortality and decrease the incidence of recurrence in carefully selected patients. The best results have been obtained when the patient meets the following criteria: a single tumor less than 5 cm in diameter, fewer than 3 tumors each less than 3 cm in diameter, and no evidence of vascular invasion, lymph node involvement, or extrahepatic metastasis[4]. The wait for liver transplantation can be up to 24 months, and at our institution averages 1 to 2 years for patients awaiting cadaveric organs. There is no clear role for neo-adjuvant treatment in these patients; however, some institutions, including ours, employ methods of local treatment, including PEI, radiofrequency ablation and chemoembolization, while patients are awaiting transplant. Currently, approximately 30 HCC patients are listed and awaiting transplant at CPMC. [5]

CP461 is a derivative of exisulind, one of a novel class of drugs called SAANDs, or selective apoptotic anti-neoplastic drugs. Exisulind inhibits growth and induces apoptosis in a wide variety of human cancer cells, including colon, prostate, breast, ovarian, pancreatic and lung [6], while sparing normal cells. Exisulind and CP461 have been shown to induce apoptosis in colon cancer cells by inhibiting cGMP phosphodiesterases 2 and 5, thereby increasing levels of cGMP, inducing PKG, and activating the MEKK1-SEK1-JNK1 cascade [7], as well as by decreasing levels of beta catenin [8]. In this study, CP461 was shown to have 100 times the affinity for cGMP PDE as exisulind.

Recent studies have shown that exisulind exhibits antiproliferative effects and induces apoptosis in HCC cell lines as well [9]. Preliminary analysis of liver biopsies taken from patients with known HCC at this institution have revealed that PDE2 and 5 are present and may be upregulated in HCC [10], as in other tumors [11], a finding consistent with the drug's effect in vitro.

Recently, a phase I clinical and pharmacokinetic trial of CP461 was conducted in 18 patients with advanced solid tumor malignancies. Patients received 100-800 mg/d. The MTD was not reached. Toxicities included asymptomatic, reversible AST/ALT elevation in one patient (grade ¾), transient sensory neuropathy in 2 patients previously treated with platinum-based agents, and alopecia in one patient [12]. The metabolism of CP461 has not been defined. For the purposes of this exercise, it will be assumed that studies in our lab have defined the IC50 of CP461 in HCC cell lines to be 3.0 +/- 1.5 uM

(experiments in progress). This concentration corresponds to a peak plasma concentration of 3.2 +/- 1.8 uM seen with a CP461 dose of 400 mg PO BID [13].

Given the very poor prognosis of HCC and the promising findings above, we will conduct a phase II randomized, double-blinded, placebo-controlled study to evaluate the activity of CP461 in HCC patients awaiting transplant. Our hypothesis is that CP461 will induce tumor regression in HCC patients as reflected in a decreased alpha-fetoprotein level and secondarily in decreased tumor burden as compared to controls. Patients must be eligible for liver transplantation at this institution and meet baseline hepatic function requirements as outlined below. Patients will receive 400 mg PO BID. Tumor response will be measured primarily by a decrease in alpha-fetoprotein levels as compared to control and secondarily by regression of tumor burden, as measured by helical CT. PDE2 and 5 levels will be measured in an initial biopsy sample and compared to tissue levels in biopsies taken at transplantation, PEI or chemoembolization.

Alpha-fetoprotein is a protein produced during gestation by the fetal yolk-sac and liver but is generally undetectable in healthy adults. However, it has been shown to be elevated in patients with HCC. Approximately 70 to 80% of patients with HCC have alpha-fetoprotein levels above 20 ug/L, and having an elevated AFP has been shown to correlate with tumor size (60% patients with HCC<2 cm vs 90% if >50% liver involved) [14]. In addition, there is a well-established and close correlation between the degree of AFP elevation and tumor size (63% HCC>5 cm have AFP>1000ug/L; 88% with HCC<5cm have AFP<1000 ug/L) [15]. In these patients, studies have shown significant decreases in alpha-fetoprotein only if an intervention reducing tumor burden is made [16]. Our lab employs an enzyme immunoassay to determine serum AFP levels. Normal values are reported as 0-8.5 ng/mL, and values are accurate to within 0.4 ng/mL (2 SD).

Objectives

The primary objective of this study is to evaluate objective tumor response to CP461 administered daily for 6 weeks in HCC patients awaiting liver transplantation. We will evaluate tumor response by following alpha-fetoprotein levels and, secondarily, by tumor size.

Secondary objectives include assessment of phosphodiesterase 2 and 5 expression in the initial biopsy samples taken from patients and comparison of initial levels with PDE 2 and 5 levels in tissue samples taken at time of chemoembolization, PEI, or transplant when available.

B. Study Design and Statistical Analysis

This study will be a phase II efficacy trial consisting of a randomized double-blinded placebo-controlled trial of HCC tumor response to CP461 in patients with elevated AFP eligible and listed for liver transplantation at CPMC.

We will employ stratified randomization in the assignment of patients. At presentation, patients' baseline AFP will be obtained. Patients will then be randomly assigned to one of three groups in each arm corresponding to initial AFP levels. Patients with an initial AFP level of >10,000 will be assigned to group A; those with an initial value of 1,000-10,000 will be assigned to group B, and those with an initial value of 8.5-1000 ng/mL will be assigned to group C[a].

CP461 will be administered to patients in the treatment arm on a twice-daily dosing regimen for 6 weeks. They will receive 400 mg PO Q12H, which corresponds to a peak plasma concentration of 3.2 +/- 1.8 uM^2. Patients in the placebo group will receive a sugar pill of similar appearance BID. After 6 weeks of treatment, patients will receive chemoembolization or PEI if clinically indicated, at which time tissue

[a] These values have been selected because of a correlation between these AFP levels and tumor size as well as survival rates seen at 60 months, with significant improvement in mortality between groups A and C and groups B and C in previous studies (see Nomura et al).

samples will be taken and analyzed for expression of PDE2 and PDE5 using immunohistochemistry. When available, these results will be correlated with clinical response.

At the beginning of the study, patients' tumor size will be evaluated by spiral CT, and baseline alpha-fetoprotein, blood chemistries, LFT's, and hematologic parameters will be obtained. Thereafter, alpha-fetoprotein levels will be obtained every other week. Patients will be monitored by bi-weekly blood chemistry testing, including AST, ALT, bilirubin, and alkaline phosphatase. Hematologic levels will be obtained every week. At 6 weeks, a spiral CT will be repeated to assess tumor response.

A patient will be considered to have responded to treatment with CP461 if their alpha-fetoprotein levels differ significantly from AFP levels in the control arm. Objective tumor response will be assessed according to guidelines validated by the RECIST criteria. Complete response is defined as the disappearance of all target lesions (all measurable lesions up to a maximum 5 lesions per organ and 10 in total); partial response is defined as at least a 30% decrease in the longest diameter of target lesions; progressive disease is defined as at least a 20% increase in the sum of the longest diameter of target lesions; and stable disease is defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease [17] . The tumor response rate will be obtained by RR= (# confirmed PR+ # confirmed CR)/# patients.

Patients will continue to receive analgesia as needed, though they will be required to record the daily amount and agent ingested

Patients may be removed from the study if a donor organ becomes available, if the patient experiences unacceptable toxicity attributable to the drug, if the patient revokes consent or is noncompliant, or if the study is discontinued.

Statistical Considerations

At least 34 patients will be enrolled in this study, 17 patients in the treatment arm, and 17 in the placebo group. Assuming an effect size equal to one SD, this sample size will give us a power of 80% with a significance level of p=0.05. This study design will allow us to reject the null hypothesis that there is no difference between arms: if no patient responds to treatment, there is a <5% chance that a positive result would be due to chance alone, and the probability of rejecting the null hypothesis when it is false is 80% (beta=20%).

Results of the two arms, both overall and between corresponding groups, will be analyzed using unpaired t-tests.

C. Study Drugs

A description of exisulind, a rationale for its use, safety and efficacy information, and toxicity is found in the introduction.

D. Medical Device

No medical devices are utilized in this study.

E. Study Questionnaires

No questionnaires are utilized in this study.

F. Study Subjects

Eligibility Criteria

- Patients must give informed consent.
- Patients must have histologically confirmed HCC.
- Patients must have an initial AFP level of >8.5 ng/mL at time of entry into the study.
- Patients must be eligible and listed for liver transplantation at CPMC. Guidelines for eligibility for transplantation include no tumor >5 cm in diameter, fewer than 3 tumors l<3 cm in diameter, and no evidence of vascular invasion, lymph node involvement, or extrahepatic metastasis as determined by Doppler ultrasound, CT of the chest and abdomen, and radionuclide bone scan. However, in certain cases, patients not meeting these criteria are listed for transplant by the liver transplant service. If these patients meet our other criteria, they will be included in the study.
- Patients may not have had chemotherapeutic treatment within 4 weeks of entry into the study.
- Patients must have measurable disease, with a minimum of one 2 cm tumor by standard CT or 1 cm tumor by spiral CT.
- Patients must have adequate organ function, as defined by
  Marrow: WBC count > 3000/uL with ANC > 1500, hg > 9 g/dL, platelets > 70,000/uL.
  Hepatic: Bilirubin $\leq$ 2.0 mg/dL, AST, ALT, and alkaline phosphatase <5 times ULN.
  Renal: CrCL > 60 mL/min
  Cardiac: No clinically significant cardiac disease.
- ECOG performance status of 0 or 1.
- No systemic infection requiring antibiotics.
- Patients must be at least 18 years old.
- Patients of reproductive age must use medically-approved contraception during treatment.

Exclusion Criteria

- Pregnant or nursing women.
- Evidence of active infection or other serious nonmalignant systemic illness.
- Psychiatric illness that could prevent the patient from giving informed consent.

G. Recruitment of Subjects

Patients will be identified by the Department of Surgery and referred to the protocol investigator. The patient's primary care physician will be contacted, and if s/he and the patient agree, the protocol investigator will explain the trial to the patient and obtain informed consent.

H. Confidentiality

All study data will be strictly confidential. Confidentiality will be ensured by the coding of patient records using a unique code. Data will be secured in the Department of Medical Oncology offices and will be accessible only to those directly involved in the study.

I. Potential Conflict of Interest

Neither CPMC nor any investigator has a proprietary interest in CP461 or might benefit financially or in any other way from the results of the investigation.

J. Location of the Study

The study will be conducted entirely at CPMC under the auspices of the Department of Medical Oncology and the Department of Surgery.

K. Potential Risks

The risks of the study are those outlined in the discussion of study design. Adverse events will be reported.

L. Toxicity

To date, no phase I trial has been conducted using CP461 in HCC patients. However, for the purposes of this exercise, we will assume that such a study has been performed and that the results are similar to the trial discussed above.

In the phase I trial discussed above, CP461 had minimal toxic effects, including reversible peripheral neuropathy in 2 patients who had received platinum-based chemotherapy, and alopecia. However, one patient developed an asymptomatic, transient elevation in AST/ALT. Given the possibility of limited hepatic reserve in these patients, we will follow LFT's very closely, as outlined above. If a patient exhibits this effect, we will modify the CP461 dosing schedule as follows:

	Transaminases X ULN		
	<2.5	>2.5 and <5.0	>5.0
Total Bilirubin < ULN	100%	75%	0
Total Bilirubin > ULN	0	0	0

For patients with either BR >ULN or AST/ALT > 5 x ULN, treatment will be withheld until the transaminases return to <2.5xULN and BR is normal [18].

Possible bone marrow and renal toxicity will be followed closely by monitoring CBC and electrolytes, as outlined above.

Other dose toxicities will be managed symptomatically whenever possible.

If a patient does not receive CP461 for 2 weeks, the patient will be withdrawn from the study.

M. Potential Benefits

It is hoped that patients involved in the study will benefit from treatment with CP461 by experiencing a decrease in tumor burden and improvement in clinical symptoms. If CP461 is shown to have an effect in HCC, phase III studies will be conducted to confirm its utility, and a novel therapy may benefit many patients who now have few therapeutic options.

N. Alternative Therapies

As discussed above, no neo-adjuvant therapy has been shown to benefit patients in terms of improving surgical outcome, preventing metastasis, or decreasing recurrence post-transplant in those awaiting liver transplant for HCC in randomized controlled trials.

O. Compensation to Subjects

No compensation, financial or other, will be provided to patients in exchange for their participation in this study.

P. Costs to Subjects

Subjects will incur no costs as a result of participation in this study.

Q. Minors as Research Patients

All patients must be over 18 years of age.

R. Radiation or Radioactive Substances

No radioactive substances will be utilized in this study.

1. Simonetti RG et al. Treatment of hepatocellular carcinoma: A systematic review of randomized controlled trials. Ann Oncol : 117-136, 1997.
2. Ibid.
3. Trevisani, F et al. Randomized Control Trials on Chemoembolization for Hepatocellular Carcinoma: Is There Room for More Studies? J Clin Gastroent 32 (5): 383-389, 2001.
4. Mazzaferro V et al. Liver Transplantation for the Treatment of Small Hepatocellular Carcinomas in Patients with Cirrhosis. NEJM 1996; 334: 693-9.
5. Personal communication, Dr. Milan Kinkabwala
6. Schmid SM et al. Growth inhibitory activity of FGN-1 and analogues in 13 human tumor lines of various histogenesis. Proc Amer Assos Cancer Res; 39: 195, a1331, 1998.
7. Soh, J et al. Cyclic GMP Mediates Apoptosis Induced by Sulindac Derivatives via Activation of c-Jun NH2-Terminal Kinase 1. Clin Canc Res 6, 4136-4141, 2000.
8. Thompson WJ et al. Exisulind Induction of Apoptosis Involves Guanosine 3', 5'-Monophosphate Phosphdiesterase Inhibition, Protein Kinase G Activation and Attenuated beta-Catenin. Cancer Research 60: 3338-3342, 2000.
9. Rahman MA et al. Sulindac and Exisulind Exhibit a Significant Antiproliferative Efect and Induce Apoptosis in Human Hepatocellular Carcinoma Cell Lines. Canc Res 60, 2085-2089, 2000.
10. Personal communication, Dr. T Kolevska and Cell Pathways
11. Piazza GA et al. Overexpression of cGMP phosphdiesterase in colonic neoplasias compared to normal mucosa. Gastroent 118:282, 2000.
12. Sun W et al. Phase I clinical and pharmacokinetic trial of the novel pro-apoptotic compound CP 461 administered orally on a continuous twice-daily schedule to patients with advanced malignancies. Proceedings of ASCO 20; 459, 2001.
13. Ibid.
14. Nomura F et al. Clinical features and prognosis of hepatocellular carcinoma with reference to serum alpha-fetoprotein levels. Analysis of 606 patients. Cancer 1989; 64: 1700-1707.
15. Ibid.
16. Matsumoto Y et al. Clinical Classification of Hepatoma in Japan According to Serial Changes in Serum Alpha-Fetoprotein Levels. Cancer 49: 354-360, 1982.
17. Therasse P et al. New Guidelines to Evaluatge the Response to Treatment in Solid Tumors. J Natl Canc Inst, 92 (3): 205-216, 2000.
18. Personal communication, Dr. T. Kolevksa and Cell Pathways. I am indebted to Dr. Kolevska for the use of this dosing regimen and table.