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A Phase I Clinical Trial of Silybin-phosphatidylcholine (Siliphos) in patients with advanced hepatocellular carcinoma (HCC)

I. Study Purpose and Rationale

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, with over 1 million cases diagnosed every year. HCC is also the 4th leading cause of cancer related deaths in the world [ACS 2008 Cancer facts and figures]. Hepatitis B and hepatitis C are the most common causes of HCC worldwide, particularly in patients with chronic active hepatitis, with hepatitis C accounting for about one third of the cases in the US. With the increasing incidence of hepatitis C in the US, the number of cases of HCC will likely continue to increase.

Patients with HCC are often grouped into one of three groups for treatment purposes: 1) localized, resectable; 2) locally advanced, unresectable; and 3) advanced, unresectable. Although HCC is a potentially curable cancer with resection, surgical treatment is often limited to the small percentage of patients with localized disease. A limited subset of patients who meet the Milan criteria (solitary tumor </=5 cm or up to 3 tumors that are </= 3cm each) may be considered as candidates for liver transplantation. Systemic treatment is usually limited to: (A) patients with potentially resectable disease, but Child Pugh C class or a poor performance status, who are otherwise ineligible for transplantation; and (B) patients with unresectable disease who are not transplant candidates and have: tumors >5 cm, multiple tumors >3cm, extrahepatic metastases, or advanced disease not otherwise eligible for other treatments.

Advanced primary liver cancer has a very poor prognosis, with estimated median survival of 6-8 months. Systemic treatment options for advanced HCC are limited and may include treatment with sorafenib, an oral multi-kinase inhibitor recently FDA approved for patients with unresectable HCC, or participation in clinical trials evaluating novel chemotherapies or combinations of chemotherapies. Chemotherapy options are often limited because of elevated liver function tests, usually secondary to underlying cirrhosis and/or tumor involvement. Elevated liver function tests can also be an adverse side effect of some chemotherapies, which can limit the dosage administered. This can also affect their effectiveness.

For patients with advanced HCC and elevated liver enzymes, there is no standard treatment, with therapies given limited to supportive care (including pain control, relief of ascites, etc), as these patients often do not tolerate chemotherapy secondary to excessive toxicity.

a. Milk Thistle

Milk Thistle (Genus Silybun Adans) is an herb that has been used for over 2000 years for purported benefits in liver and biliary diseases. Traditional milk thistle extract is made from the seeds and is composed of 65-80% silymarin and 20-35% fatty acids [Kroll 2007]. Silymarin is the main active constituent of milk thistle (MT). Silymarin is a mixture of polyphenols including flavonolignans and flavonoids. Silybin (also known as silybinin or silibin) is the main flavonolignan of silymarin and in traditional extracts makes up 60-70% of active silymarin [Kroll 2007, Hogan 2007]. Other flavonolignans present in silymarin include: isosilybin, silychristin, and silydianin.

Silymarin has shown to be hepatoprotective in numerous in vitro studies evaluating cell exposure to various toxins including acetaminophen, carbon tetrachloride, galactosamine radiation, iron overload, ter-butyl hydroperoxide, phenylhydrazine, phaloidin, thioacetamide, and thallium. Studies have evaluated possible mechanisms by which silymarin may be hepatoprotective, and have found that it has a broad range of biological effects including a being a potent anti-oxidant that can scavenge or neutralize free radicals, reduce or inhibit lipid peroxidation, chelate metals, and stabilize cellular membranes. It may also help prevent toxin entry into cells or possibly be involved with toxin exportation. Its purported mechanism of hepatoprotection may also include modulation of both phase I and phase II detoxification pathways in a dose dependent manner [Zuber 2002, Venkataramanan 2000]. In in vivo mice models, silymarin was shown to stimulate the phase II detoxification pathway, increasing levels of glutathione and glutathione S transferase, in a dose dependent manner in several tissues, including liver, lung, stomach, small bowel, and skin [Zhao 1999].

b. Studies of MT use in Humans

MT is widely available as an herbal or dietary supplement in the US and abroad. In the United States, surveys have found milk thistle to be the most common agent for purported hepatoprotection used by patients visiting gastrointestinal clinics [Flora K 1996, Flora 1998]. Silymarin is currently not FDA approved in the US for any medical conditions.

In humans, MT has been used as an antidote for mushroom poisoning with Amanita phalloides, which can cause liver failure with significant mortality [Hruby 1983]. The German E commission has approved MT use for dyspepsia, toxin induced liver damage, hepatic cirrhosis, and as supportive therapy for chronic inflammatory conditions [Blumenthal M 1998].Milk thistle has also been evaluated in patients with acute, subacute, and chronic hepatitis, including both alcohol related and viral induced hepatitis. There has been conflicting evidence in these studies as to the effectiveness of MT as a treatment agent. In a recent Cochrane review evaluating milk thistle for alcoholic and/or Hepatitis B or C liver diseases [Rambaldi 2005], a meta-analysis of 13 randomized clinical trials (for which data was available), was completed and found that MT versus placebo or no intervention had no significant effects on all cause mortality (relative risk (RR) 0.78, confidence interval C.I. 95% 0.53-1.15) or complications of liver disease. However, overall liver related mortality was significantly reduced by MT use (RR 0.50, 95% C.I 0.29-0.88). MT use was also found to have decreased bilirubin and GGT activity. Evaluation of clinical data has been confounded by several factors including use of different formulations and doses of MT extracts, which can vary greatly by silybin content.

c. Studies of MT use in Cancer Models

Silymarin and silybin use have been studied in several cancer cell line models including: prostate cancer cell lines (DU 145, LNCaP, PC-3), mouse skin cancer model, breast (MDA-MB 468, MCF-7), hepatic cancer (HepG2), epidermoid (A431), colon (Caco-2), ovarian (OVCA 433, A2780), histiocytic lymphoma (U937), and leukemia cells (HL-60). Silymarin use in various animal cancer models include: skin, tongue cancer, bladder cancer, colon adenocarcinoma, and small intestine adenocarcinoma.

These studies have shown that silymarin may have direct anti-neoplastic effects by inhibition of growth factors and cell signaling involved in cell growth stimulation; inhibition of anti-apoptotic activity; and promotion of cell cycle arrest. In in vivo animal models, silymarin has also been shown to reduce the size and number of tumor masses and reduce metastases [Provinciali 2007].

d. Evaluation of Milk Thistle in Human Subjects with Cancer

The anticancer effects of MT seen in multiple cancer cell lines and animal models, and the reductions in LFTs seen in several studies in patients with hepatitis, suggest that there may be benefits of MT use in cancer patients either as adjunctive anti-neoplastic therapy (directly or by potentiating the effects of chemotherapy), or adjunctive therapy in reducing baseline LFTs prior to chemotherapy, or in reducing hepatotoxicity associated with chemotherapy.

There are at least 3 clinical studies of MT use in patients in cancer that we are aware of (2 published, 1 manuscript in submission; Elena Ladas, communication). In the study by Flaig et al, a phase I study in patients with prostate cancer was completed to find the safety profile and maximum tolerated dose for direct anticancer effects using a silybin-phytosome complex [Flaig 2006] using a dose range of 2.5 to 20 gm over a four week duration. The most prominent adverse effect seen in the study was hyperbilirubinemia, with grade 1-2 bilirubin elevations in 9 of the 13 patients. The authors concluded that 13 g of oral silybin-phytosome was well tolerated in these patients. In a pilot study in patients with primary colorectal adenocarcinoma with hepatic metastases evaluating the safety and pharmacodynamics of MT, Silipide (silibinin phosphatidylcholine, 1:1 molar ratio) was given at dosages of 360, 720, or 1440 mg silibinin daily for 7 days. Blood, colorectal, or hepatic tissues were collected at the time of resection and compared to biopsy samples taken prior to silibinin dosing. Plasma levels were related to silipide dosing and similar to levels identified from the manufacturer in healthy volunteers. They also found that MT was well tolerated in their study [Hoh 2006]. In a pilot phase III study currently ongoing at Columbia (Kara Kelly, PI), investigating the efficacy of milk thistle versus placebo in the treatment of hepatotoxicity in children undergoing maintenance chemotherapy in ALL, there were no significant differences in the frequency of side effects, incidence or severity of toxicities between the two groups [Elena Ladas, personal communication].

e. Study background summary and purpose of current study

Advanced HCC has a poor overall prognosis, often determined by the degree of underlying hepatic dysfunction. Patients with advanced HCC or locally advanced unresectable HCC have limited treatment options including participation in clinical trials, or more recently, treatment with sorafenib, which has been FDA approved as the first line systemic therapy for advanced HCC. Treatment with sorafenib or other chemotherapeutic patients may be limited in patients with elevated liver function tests at baseline or as a result of chemotherapy toxicity. Thus it would be beneficial to identify adjunctive therapies that may reduce liver function tests. Milk thistle, with silymarin as its active constituent, has been shown to have hepatoprotective properties in multiple in vitro studies and in animal models. Silymarin may also have direct anticancer effects. Although there is conflicting evidence of the efficacy of silymarin and overall mortality in chronic hepatitis, it may reduce liver-related mortality. Several studies have shown that it may help improve or normalize liver function tests in patients with underlying liver disease. MT also has an excellent safety profile with mimimal adverse side effects.

To our knowledge, there have been no clinical studies of MT use in patients with HCC. We hypothesize that treatment with silymarin in patients with HCC will reduce liver function tests, compared to baseline, which may allow anticancer treatment to be given. Treatment with MT in these patients may also improve symptoms related to elevated liver function tests, including fatigue and pruritis.

We therefore propose a phase I dose finding study to identify the safety profile and maximum tolerated dose of MT in patients with advanced HCC with elevated liver function tests, with intentions to utilize this data in future studies to evaluate whether MT can reduce liver function tests in this patient population and improve quality of life measurements, which will have significant implications in its use as a potential adjunctive agent in patients with currently very limited treatment options.

II. Study Design

This study utilizes a standard combination phase I open label dose escalation design to define the maximum tolerated dose (MTD) and safety profile of milk thistle in subjects with advanced HCC and elevated liver function tests over a three month active study medication duration period, and one year follow-up. The total number of subjects will be 24, with recruitment goals of at least one HCC patient per week. The MT dose levels that we will study include: one gram, four grams, eight grams, and 10 grams (gm) daily. The Siliphos formulation of MT (1:2 ratio of silibinin to phosphatidylcholine) in powder form will be utilized.

a. Description of treatment regimen

This study will follow a sequential dose escalation design. The following dose escalation rules will be used:

- Three patients will be accrued at each dose level
- If no dose limiting toxicity is seen at this dose level after three weeks of treatment, the next cohort will receive the next highest dose level. If one of the three patients experiences a dose limiting toxicity (DLT), three additional patients will be treated at that dose level.
- If no further patients experience DLT, the dose will be escalated to the next higher dose for the following cohort. If one or more additional patients experience a DLT, then the MTD has been exceeded and the dose will be decreased to the next lower cohort dosage for those particular patients.

The MTD will be defined as the highest dose at which fewer than 2 of 6 patients experience DLT. A total of 6 patients will then be treated at the MTD. At this point more patients will be treated at the MTD dose level to a total of 24 subjects to obtain further toxicity information. Subjects in dose level 1 who develop DLT will be discontinued from the study. Subjects in subsequent dose levels (>1) who develop DLT may continue study therapy after the dose of the study drug has been decreased. If subjects discontinue the study prior to the completion of the first dose level of study treatment for reasons other than dose limiting toxicity, new subjects will be enrolled.

a. Definition of DLT

Adverse events and abnormal laboratory values will be graded using the National Cancer Institute (NCI) Common Terminology criteria for adverse events (CTCAE version 3.0). For the purposes of determining the MTD during the treatment phase, DLT is defined as any one of the following:

- >Grade 3 non-hematological toxicity excluding alopecia; and excluding nausea, vomiting, diarrhea, headache, urticaria, rash or constipation, if they can be controlled with supportive medications
- Febrile neutropenia (absolute neutrophil count <1000/ul and fever >101 degrees F).

- Grade 4 neutropenia
- Platelet count <25, 000/ul

b. Endpoints of the Study and Statistical Analysis

The primary endpoints of this study are to:

1) Identify the maximum tolerated dose of MT in patients with advanced HCC
2) Evaluate the safety profile of MT in patients with advanced HCC including type, frequency, severity of adverse events and their relationship to study drug

Secondary analyses will include:
1) Determination of the mean percentage change in liver function tests (including total bilirubin, AST. ALT) in each dose category and intra-patient changes compared to baseline; a 25% change will be considered significant
2) Quality of life differences comparing each dose category using the previously validated FACT-hepatobiliary questionnaire
3) Determination of the mean peak serum level of MT in each dose category at weeks 1, 3, 6, 9, and 12 (blood sample will be taken 1-2 hours after the morning dose on the day of collection)
4) Determination of the % change in mean serum levels of CRP, glutathione S transferase and maldehyde dehydrogenase compared to baseline over time
5) Change in intra-patient tumor size using RECIST criteria
6) Change in intra-patient AFP levels compared to baseline
7) Comparison of mean percentage change in liver function tests in cirrhotic versus non-cirrhotic patients with HCC
8) Comparison of mean percentage change in liver function tests or tumor response in patients with hepatitis B versus hepatitis C, as HCC tumor pathophysiology varies between the two conditions

These secondary endpoint exploratory analyses will help guide preparation for a larger, randomized control study of adjunctive MT in advanced HCC. The sample size of 24 patients for this study is based on the standard dose escalation design used for phase I studies to identify the MTD by identifying DLT. Importance of close follow-up will be emphasized to all potential participants prior to enrollment. Since all patients will be treated at Columbia, we anticipate close follow-up.

III. Study Procedures

Patients who meet study criteria and provide informed consent will be enrolled in the study. Baseline variables will include a basic history and physical, baseline laboratories (liver function tests, AFP, hsCRP, maldehyde dehydrogenase, glutathione S transferase) taken at day 0 (prior to start of study medication which will be day 1), completion of the FACT hepatobiliary QOL questionnaire, completion of an additional questionnaire with demographic and medical history, and have imaging within two weeks of enrollment (MRI abdomen/pelvis; CT Chest).

During the course of the study, study labs will be assessed at weeks 1, 3, 6, 9, and 12 during active treatment, with duration of active treatment being 12 weeks. Imaging with MRI of the abdomen and pelvis and CT Chest will be obtained every 3 months. Study subjects will complete the FACT QOL questionnaire at weeks 1, 6, and 12 during active treatment. Patients will be monitored for adverse effects during clinic visits at weeks 1, 3, 6, 9 and 12 during active treatment. Safety variables will include a complete review of systems at each clinic visit while on study, according to CTCAE criteria. A pill count will be completed at each clinic visit to evaluate compliance with study medication. A urine pregnancy test will also be completed prior to initiation of study medication for women of child bearing age (18-65) and at week 6 during active treatment, as pregnant women will be excluded from the study due to the lack of information of possible adverse effects in pregnant women and fetuses by MT use. The Columbia chemotherapy pharmacy will allocate the specified dose of study medication to each study subject. Study subjects will be followed until one year after last dose of study medication or until mortality, whichever comes first, for continued evaluation of secondary endpoints and continued toxicity assessment. All laboratory data and study visit data will be collected on paper case report forms (CRFs). The PI or her data manager will input the data into a secure electronic database.

IV. Study Drug/Devices

Traditional milk thistle extract is composed of 65-80% silymarin and 20-35% fatty acids. Silybin is the main flavonolignan of silymarin and constitutes 60-70% of active silymarin in traditional extracts [Kroll 2007]. The form of MT that we will be using in this study is silybin-phytosome or Siliphos, a lipophilic formulation in which silybin is complexed to soy phosphatidylcholine. Siliphos contains 33% silybin by weight [Indena corp manufacturing, Thorne corp distribution]. In this phase I study, we will evaluate 4 doses of Siliphos: 1 gm, 4 gm, 8 gm, and 12 gm to be taken in three divided doses daily. It will be obtained as a powder and mixed with applesauce at a ratio of ¼ teaspoon of siliphos to 1 tablespoon of applesauce. Subjects will be directed to take the specified dose three times daily, at least 30 minutes before meals. The Columbia chemotherapy pharmacy will allocate the specified dose of study medication to each study subject. The powder will be stored in its original container at controlled room temperature. Representative samples from the batch will be tested at 6 month intervals to ensure stability. An application for an IND for the use of Silybin as adjunctive treatment for subjects with HCC will be underway, under PI Dr. Abby Siegal.

V. Study Questionnaire

Subjects enrolled in this study will complete a baseline questionnaire with demographic information and their medical history at day 0 prior to initiation of active study drug. Subjects will also complete the previously validated FACT hepatobiliary quality of life questionnaire at baseline and at weeks 1, 6, and 12 during active study treatment and at one year. Both questionnaires are attached in the addendum section.

VI. Study Subjects

This study will enroll a total of 24 subjects. Both men and women, and members of all ethnicities are eligible for this trial. This trial will be limited to adults (age>18) as HCC is a disease primarily of adults.

Inclusion Criteria:

- Age >18 years
- ECOG performance score of 0-3
- expected survival of >12 weeks
- Subjects with advanced HCC or locally advanced, unresectable HCC who are ineligible for other systemic treatment because of ECOG performance, elevated LFTs or Child Pugh Class B/C
- Elevated LFTs (including at least one of the following: TBili >1.5 times the upper limit of normal; serum AST >2.5 times the upper limit of normal; ALT >2.5 times the upper limit of normal)
- HCC has to be diagnosed/defined based on either biopsy, or by suggestive radiologic imaging (arterial enhancement with venous washout) plus an AFP >200 ng/ml
- Elevated liver enzymes that are either due to underlying liver disease and/or tumor which is not amenable to stenting after discussion with interventional GI and/or IR
- No previous systemic therapy
- Subjects must agree to use birth control pills or other active contraception during active study treatment

Exclusion Criteria

- Pregnant women or women currently breastfeeding will be excluded from this study because the effects of silymarin on pregnant women and/or nursing infants are not known
- Subjects cannot receive other investigational agents simultaneously
- Subjects must be free from other HCC treatment for at least 2 weeks
- Known brain metastases because of poor prognosis and as patients with brain metastases often develop neurological dysfunction that may confound evaluation of neurologic and other adverse side effects
- History of allergic reactions to the study medication
- Uncontrolled concurrent illness including, but not limited to: ongoing active infection (including SBP), symptomatic congestive heart failure, unstable angina, active cardiac arrhythmia, or psychiatric illness that would limit compliance with study requirements

VII. Recruitment

Direct person to person contact in a medical setting will be used to identify prospective subjects. We anticipate that the majority of patients will be recruited from the GI oncology clinic of the principal investigator or from

inpatient medicine services. If we fall short of our recruitment goals after the first two months of the study, we will invite our collaborators at Cornell and NYU to help with accrual.

VIII. Study Data Collection, Storage, and Confidentiality

Blood samples, data sheets, and questionnaires will be given unique study identifiers not associated with personal identifiers. The researchers will maintain a list of the codes in a locked drawer, accessible to the PI, and designated study personnel only. Blood samples will be given for banking through the Columbia tissue banking center using unique codifiers not associated with personal identifiers. Designated data sheets and questionnaire data will be maintained for 10 years after study conclusion.

IX. Potential Risks and Adverse Events

The potential risks of participating in this study include reactions to the study medication, and the risk of bleeding or infection at the site of blood draws. Pregnant and breast feeding women will be excluded from this study as there are no adequate studies of MT in pregnant or lactating women. Subjects will also receive the standard of care for advanced HCC as determined by the treating physician which can have inherent risks not related to the study itself.

To our knowledge, there have been no previous studies of MT use in patients with HCC. However, patients with HCC often have underlying cirrhosis or other liver disease. MT has been found to be well tolerated in patients with varied underlying liver disease, with no or limited adverse events reported using a range of MT doses including patients with chronic liver disease of mixed etiology [Realini 1975, Lirussi 1995, Tanasescu 1988] and acute viral hepatitis [Tkacz 1983, Flisiak 1997].

In a phase II randomized, open label study by Vailati et al (1993) [Vailati 1993], evaluating MT use (Silipide, a silybin-phosphatidylcholine formulation of MT similar to Siliphos; doses 160 mg, 240 mg, 360 mg) over two weeks in 60 patients with chronic alcoholic or viral hepatitis, a total of 6 adverse events were reported including: nausea, heartburn dyspepsia (160 mg dose, 3 patients); dyspepsia (240 mg, one patient);nausea and meteorism (360 mg, 2 patients).

In the recent Cochrane meta-analyses of 13 randomized control trials evaluating MT for alcoholic and or hepatitis B or C related liver disease [Rambaldi 2005], 0/456 patients had serious adverse events versus 0/459 in the control group. They also found that MT did not significantly affect the occurrence of non serious adverse events (16/456 in MT group versus 20/459 in control group, RR 0.83, CI 0.46-1.50). Adverse events reported included pruritis (4 patients), cephalea (three patients), nausea (one patient), impotence (1 patient). Other studies have also reported non-serious adverse effects including diarrhea, mild dizziness, and pruritis [Saller 2001, Gordon 2006]. Mild allergic reaction and anaphylaxis have been reported but are exceptionally rare [Geier 1990, Mironets 1990].

In summary, MT appears to be well tolerated, with a limited adverse event profile compared to placebo, with GI effects such as mild diarrhea, being most commonly reported. All serious adverse events reported by patients during active study treatment or follow-up will be reported to the IRB and DSMB at Columbia within 24 hours of occurrence for assessment. Proper phlebotomy techniques will be used to minimize risks of infection and bleeding from blood draws.

X. Potential Benefits

There are currently no studies of MT use in patients with hepatocellular carcinoma. Therefore, individual participants may not directly benefit from participating in the study. This information will be used in phase III studies to evaluate whether MT use can reduce elevated LFTs and allow patients to have more therapeutic options. Therefore, future benefits to patients with HCC include elucidating the MTD and safety profile of MT, which will help determine doses used to evaluate its effectiveness in lowering LFTs in HCC patients in the future.

XI. Alternatives

Regardless of participation in the study, all patients will receive the care appropriate for their advanced HCC by the treating physician. Alternatives to participating in this research study include not participating.

Risk to benefit ratio
Patients with advanced HCC have a poor prognosis. Patients with concomitant elevated LFTs have further limited systemic therapy options, and often have no alternative therapy available. This study will help identify the MTD and safety profile of MT in patients with HCC, the results of which will be used in the future for a phase III trial to determine if MT can decrease elevated LFTs in this patient population and/or have direct anti-cancer properties.

In the setting of a limited MT adverse profile, we therefore anticipate that the possible benefit to this class of patients far outweighs the potential risks undertaken by individual study subjects as well as the alternative of doing nothing.

XII. Subject Compensation/Justification

Payment for Participation: Subjects will not be compensated for participation, but the study drug will be provided free of charge.

Financial Obligations of the Subjects: Subjects are not anticipated to incur any costs related to participating in this study, and will only be responsible for costs incurred from routine standard of care, through the treating physician.

Emergency Care and Compensation for Research-Related Injury: If subjects are injured as a direct result of research procedures, they will receive treatment at no cost, and no other form of compensation for injury, as per Columbia University policies stated in the consent form.

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