Phase II Trial: Therapy of Pleural Malignant Mesothelionta with ST1571 and Cisplatin

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A. Statement Of Purpose And Rationale

a. Objective

This is a phase 11 study of a new chemotherapeutic agent ST1571 (Gleevac), a tyrosine kinase inhibitor, and cisplatin, which is a conventional agent in the therapy of pleural malignant mesothelioma (MM). In Part 1, we will determine if ST1571 monotherapy has significant activity against M[M. If ST1571 is ineffective as monotherapy, Part 11 will determine if combined therapy with ST1571 and cisplatin yields response rates superior to monotherapy.

b. Background on Tumor

Malignant mesothelioma has an annual incidence of 2200 cases/year in the US (1). 50% to 70 % of cases can be linked to prior asbestos exposure. Approximately 2/3 of cases are pleural, and 1/3 of cases are peritoneal. In pleural disease, the tumor usually grows in the space between the parietal and visceral pleura, and forms a hardened rind that encases the lung. Median survival from time of diagnosis is about 12 months. Death is usually due to respiratory failure or pneumonia (1). Poor prognosis is associated with male gender, histological subtype (sarcomatous is worse than epithelial subtype), performance status at baseline, and elevated white blood cell count (2).

Mesothelioma remains difficult and frustrating to treat, with no conclusive studies to date demonstrating any significant impact of surgery, radiotherapy, chemotherapy, or combined modality treatment on survival (3). No single chemotherapy agent produces response rates greater than 20% in large scale trials. Expert review of the literature of cisplatin trials with 59 patients in total finds that the response rate is about 14% (3). Some small studies of combined chemotherapies report response rates from 3 1% to 48% (4, 5). This needs to be verified in larger trials. None of these regimens have been widely accepted.

c. Rationale for New Therapy

Receptor tyrosine kinases are signaling molecules that are inappropriately activated in some malignancies (6). The receptors activate signal transduction pathways that drive the proliferation of malignant cells. An emerging concept in chemotherapy is the design of drugs that selectively inhibit signaling molecules such as receptor tyrosine kinases.

STI-571 is a selective inhibitor of three tyrosine kinases: c-abl, c-kit, and the PDGF receptor (7). The BCR-ABL oncogene is the molecular hallmark of chronic myelogenous leukemia (CM[L). It produces a constitutively active bcr-abl kinase. Inhibition of bcr-abl kinase with ST1571 is effective in CM[L with responses documented in 53 of 54 patients in the chronic phase and 21 of 3 8 patients in the blast crisis phase (8,9).

STI-571 is FDA-approved for use in CM[L, and evidence is accumulating that it may be useful in other malignancies as well. STI-571 inhibition of c-kit induces clinical responses in gastrointestinal stromal cell tumor (10,11). In an animal model of Dermatofibrosarcoma protuberans, blockade of the PDGF receptor with high levels of ST1571 induces tumor regression (12).

The PDGF receptor is a widely expressed tyrosine kinase that may be a useful therapeutic target in malignant mesothlioma. High levels of PDGF receptor expression occur in the CNS, sites of wound healing, and many tumors (13). The receptor is composed and α and β subunits, which join to form homodimers (α/α, β/β) and heterodimers (α/β). The PDGF-A ligand binds all three dimers, while the PDGF-B ligand only binds the β/β isoform. The three dimeric PDGF receptor combinations transduce

overlapping, but not identical, cellular signals which contrl proliferation, cell survival, chernotaxism and apoptosis (13). Most information is available about the function of the PDGF receptor homodimers. Activation of the β/β isoform. stimulates chernotaxis, while activation of the &a receptor inhibits chemotaxis. The PDGF β/β receptor is more effective at increasing intracellular calcium than is the PDGF a/a receptor. (13). There may be other signaling properties unique to the different isoforms of the receptor.

Some pre-clinical work suggests that the PDGF receptor may be important in pleural mesothelioma. In fibrotic lungs exposed to asbestos, PDGF production by macrophages is upregulated (1). PDGF receptor expression has been reported in 15/15 pleural biopsy specimens of malignant mesothelioma patients (14). A comparison of mRNA from 12 malignant mesothelioma cell lines with mRNA from normal mesothelial cell lines suggests that in malignancy the β/β isoform of the PDGF receptor is upregulated, and the a/a isoform is strongly downregulated (15). Malignant mesothelioma cells from pleural effusions expression of PDGF-B, the ligand for the PDGF β/β receptor (15). Another study finds that MM cell lines transcribe PDGF-B mRNA and secretete functional PDGF, while normal mesothelial cells to not (16). One might hypothesize that in pleural mesothelioma cells, proliferation is driven by an autocrine loop involving PDGF-B and the PDGF β/β receptor. Blockade of the PDGF receptor by ST1571 is an appealing strategy for therapy of malignant mesothelioma.

If ST1571 fails as monotherapy for MM, it may be useful in a combined chemotherapy regimen. A recent study in mice suggests that STI-571 may improve delivery of other chemotherapeutic drugs to cancer cells. In mice with transplanted colon cancers that are PDGF receptor-negative, treatment with ST1571 decreases interstitial pressure (IFP) in tumors and allows increased tumor uptake of a radiotracer molecule (17). The authors propose that increased IFP in tumors may limit delivery of chemotherapeutic agents to malignant cells, and that PDGF β/β receptors in stromal fibroblastoid cells help regulate IFP by exerting tension on the collagen/microfibrillar network. In theory, strategies using ST1571 to decrease IFP could enhance delivery of other chemotherapeutic agents to the malignant cells. One hypothesis is that ST1571 might allow improved delivery of cisplatin to tumor cells in MM.

Part I of this study will first test the hypothesis that ST1571 monotherapy can induce clinical responses in MM by blocking an autocrine loop involving PDGF-B and the PDGF β/β receptor. If this therapy fails, Part 11 of the study will test the hypothesis that STI-571 improves tumor uptake by cisplatin, achieving response rates superior to those of cisplatin alone.

B. Study Design And Statistical Analysis

a. Primary and Secondary Endpoints

The primary endpoint will be response rates with combined therapy as determined by change in tumor burden on CT scan. Complete response (CR) is the absence of disease on CT scan. Partial response (PR) is defined as at least 50% reduction in the sum of the products of the perpendicular diameters of all tumor diameters (ie, tumor area). CR and PR should persist for at least 4 weeks. No change (NQ is defined as a reduction of less than 50% or an increase of less than 25% of tumor area. Disease progression is an increase by more than 25% in the tumor area or as the appearance of a new lesion.

A secondary endpoint will be change in tumor burden on PET scan. A difficulty with CT scan use in previous trials is that pleural MM grows like a rind around the lung, which complicates accurate measurement of tumor area. PET scanning with ^{18}Ffluordeoxyglucose in malignant mesothelioma may have prognostic significance. A recent study of 28 patients with pleural MM finds that radiotracer uptake on PET scan correlates directly with survival (18). PET scanning will not be required of patients in this study due to availability and expense, but it will be performed in as many patients as possible.

Other secondary endpoints include survival, performance status, PFT results, response rates by PDGF-receptor status and EGF receptor status, response by histological subtype, and toxicities of the study drugs.

b. Statistical Analysis

Data will be analyzed by the Chi-Squared method.

In Part 1, a response rate >= 30% would be clinically significant. An interim analysis will be performed after 12 patients have been studied for three months. Study design models indicate that if 0 or I of the first 12 patients have clinical responses, monotherapy can be stopped with an error probability <= 0.1 of rejecting a drug with a response rate of >=30% (19). If 2 or more patients respond at the interim anaysis, Part I will be continued until 35 patients have accrued. If <=5/35 patients respond, the drug is rejected with an error probability <=O. I of rejecting a drug with a response rate >=30% (19).

In Part 11, all patients will receive cisplatin and ST1571. Historical controls for response rates to cisplatin alone will be used. Expert review of the literature of cisplatin trials with 164 patients in total puts the response rate at 14% (3). A clinically meaningful result for combined therapy in this study would be an increase in response rate to 40%. Patients in this study will be compared to historical controls in terms of age, gender, performance status, and histologic subtype.

A study design model will determine the number of patients needed in a phase 11 trial using historical controls (19,20). The model incorporates variables for historical control rates, number of historical control patients, and target level of response rate with combined therapy. This model indicates that 24 patients would be needed for 80% power with a 5% one-sided significance level to find a response rate of 40% with combined therapy. For two-sided significance, 30 patients would be needed.

C. Study Procedure

In Part 1, patients will receive ST1571 800mg orally per day in two divided doses. In Part 11, patients will receive cisplatin 90Mg/M2 bolus infusion every four weeks and ST1571 800mg orally per day in two divided doses. CT scanning will be performed at study entry, and every 28 days thereafter. Initial assessment, safety monitoring and other data collection, and dose adjustments are described elsewhere in this report.

D. Study Drugs And Toxicities

a. ST1571 (Gleevac):

In a phase I trial of the drug with 83 patients, adverse effects were generally mild to moderate. Patients were assigned to receive doses from 25mg to I gram per day. A maximal tolerated dose was not identified (8). The most common side effects included nausea (43% of patients), myalgias (41%), edema (39%), and diarrhea (25%). Most adverse effects, even at the highest doses, were mild or moderate. Severe neutropenia and thrombocytopenia occurred in 14% and 16% of patients, respectively. Mild transient anemia was common. Moderate to severe elevations in liver enzyme levels occurred in 8% of patients. One patient discontinued the drug due to a recurrence of angina, and another due to persistent and progressive rash.

b. Cisplatin (Platinol):

Nephrotoxicity is dose limiting for cisplatin administration (21). This dose-dependent nephrotoxicity causes a rise in serum creatinine or BUN peaking 10-15 days after therapy. Various hydration schedules have been used effectively as prophylaxis. Nausea and vomiting are characteristically severe and prolonged. Various hydration Thrombocytopenia and leukopenia are usually mild. High frequency hearing loss, tinnitus and occasionally deafness may occur. Peripheral neuropathies (paresthesias or sensory loss in a glove/ stocking distribution or as muscular weakness) increase with increasing cumulative dose. Anaphylactic reactions have been reported which require epinephrine, antihistamines, and cortico steroids.

E. Eligibility Criteria

Patients must fulfill the following Inclusion criteria: histologically confirmed pleural malignant mesothelioma, age greater than 18 years; life expectancy greater than 3 months, informed consent, good performance status, and adequate laboratory data.

Required initial laboratory data:

White cell count	>3000/ul
Platelet count	>100,000/ul
BUN	< 1. 5X normal
Creatinine clearance	>60ml/min
Bilirubin, AST, ALT	<1.5X normal

Exclusion criteria are: significant pleural effusions on chest X-ray, serious psychiatric illness preventing informed consent, prior chemotherapy or radiotherapy, prior malignancy, pregnancy or lactation.

F. Safety Monitoring And Dose Adjustments

Safety assessments will include initial history and physical, EKG, and chest X-ray prior to entry into the study. CBC, chem-12, liver function tests, chest X-ray, and urinalysis will be performed weekly.

Mild to Moderate hematologic toxicity can occur with ST1571. If absolute neutrophil count (ANC) drops to <500/mm3, treatment with ST1571 will be interrupted until the ANC rises to >1000/mm~. ST1571 will then be restarted with the daily dose reduced by 200mg per day. Prolonged neutropenia may require support with G-CSF. Similar dose adjustments will be made for thrombocytopenia and blood products will be given as necessary.

Mild elevations of LFTS in patients taking ST1571 usually resolve spontaneously. Persistent elevations of LFTS require holding of ST1571.

Cisplatin-induced renal toxicity will be monitored closely. If the creatinine clearance decreases to < 40 ml/min, the next dose of cisplatin will be omitted. For a creatinine clearance is between 40 and 60 ml/min, reduce the cisplatin dose by 50%.

Cisplatin dose will be decreased by 50% for moderate neurotoxity, such as paresthesias. The next dose of cisplatin will be help for severe neurotoxicity, such as weakness. The occurrence of these adverse effects should be low at these doses.

G. Removal From The Study

Patients will be removed from the study for:

- Progression of Disease
- Development of significant Pleural Effusions
- Persistent elevations in LFTs despite dose adjustments as above
- Persistent hematologic toxicity despite supportive therapy
- Sever nephrotoxicity or neurotoxicity despite cisplatin dose adjustments

H. References

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INFORMED CONSENT

INTRODUCTION

You are invited to take part in a research study to determine the effectiveness of a new chemotherapy regimen for your pleural mesothelioma tumor, which we hope will arrest the growth of the tumor. Your physicians feel that your tumor will continue to grow without effective treatment. Because of these problems, we are always in search of new treatments that may be effective. The proposed treatment involves a new chemotherapy drug, Gleevac (ST1571). Gleevac has not been tested yet in mesothelioma, although it is effective in other tumors. At the discretion of The Principal Investigator, some patients may also receive Platinol (Cisplatin) in addition to Gleevac. In the past, Platinol given alone has reduced tumor size in about 14% of patients. Some patients in this study may receive both Gleevac and Platinol to determine if combined therapy is more effective than therapy with one drug alone.

It is important that you read and understand several general principles that apply to all who take part in this study: a) this is a research study and taking part in the study is entirely voluntary, b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others, and c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the potential risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the staff members who will explain it to you.

PROCEDURES

If you decide to participate, you will receive chemotherapy with Gleevac, which will be given by 2 pills daily. For some patients. Cisplatin may be given by intravenous infusion on day I and every 28 days thereafter. All of the above will be given on an outpatient basis.

Your doctor will evaluate you initially, at 2 weeks, at 4 weeks, and then monthly during treatment. The initial evaluation will consist of three (3) blood tests (3 teaspoons of blood), a chest X-ray, tomographic X-rays ("CT scans") of the chest, an electrocardiogram, and urine tests. During treatment, your blood tests will be repeated at least weekly. CT scans of the chest will be repeated every four weeks.

RISKS OF CHEMOTHERAPY

Bone Marrow suppression (Gleevac) Blood cells are made in the bone marrow and are responsible for fighting infection (white blood cells), carrying oxygen (red blood cells) and causing blood to clot (platelets). A reduction in the number of these blood cells (marrow suppression) can lead to an increased risk of bleeding and infection. Should these effects occur, they can be treated with blood products (transfusions) and antibiotics. Gleevac dose may be reduced or held at physician's discretion.

Nausea and vomitiLig: loss of ygpetite (Platinol, Gleevac) Although some patients may have no nausea and vomiting, some will experience some nausea and several episodes of vomiting. For some patients, vomiting will be more severe and more prolonged. Antinausea medications will be prescribed if yon need them.

HeariM Lo : (Platinol) Hearing loss may occur, most often in the higher tones (above the usual speech range). Eventually a hearing aid may be required if there is progressive hearing loss.

Liver toxici : (Gleevac) In some patients, blood tests have indicated that alterations in liver chemistry have occurred during therapy with these drugs. These were usually unassociated with any symptoms, and were usually rapidly reversible after the dose of drug was reduced.

Kidney toxiciV: (Platinol) In some patients, kidney damage has been reported, with fluid retention and change in concentrations of salts in the blood. Rarely, severe failure of the kidneys with a need for dialysis or kidney transplant, has occurred. Your physicians will take extra precautions in the form of frequent monitoring with blood tests to guard against serious kidney damage.

Neurological Toxi!~.- (Platinol) In some patients high frequency hearing loss, ringing of the ears, and occasionally deafness may occur. Peripheral neuropathies (numbness or sensory loss in a glove/ stocking distribution or as muscular weakness) increase with increasing cumulative dose.

UNANTICIPATED SIDE EFFECTS may occur which have not been reported. If you have any unusual symptoms, report them immediately to your physician.

BENEFITS

The possible benefit for persons receiving this treatment (if it is found to be effective) is reduction in the size of the tumor and overall lengthening of your survival. However, your doctors cannot and do not guarantee that you will benefit if you participate in the study. In addition, the information which is obtained may he useful scientifically and possibly helpful to others.

ALTERNATIVES

Patients with pleural mesothelioma often, but not always receive some type of therapy to delay disease progression. There may be other treatments for your cancer such as other chemotherapy with other drugs, radiation therapy, surgery, or a combination of the above. Currently used other drugs for therapy of malignant mesothelioma include doxorubicin, mitomycin C, and ifosfamide, used intravenously or intrapleurally, singly or in combination, which may help shrink your tumor with significant side effects. Their relative usefulness in your situation cannot be determined with certainty. An additional alternative is no therapy. Your doctor will discuss the benefits and side effects of alternative treatments. If new significant findings concerning your disease or treatment become known while you are on study, your doctor will discuss them with you.

STUDY TERMINATION

Your participation in the study may be terminated by your doctor without your consent if you are not benefiting from the treatment or if it is determined that the treatment is not appropriate for your condition or for other reasons at his/her discretion. This study may be terminated by your doctor, by the Presbyterian Hospital, or by Columbia University for any reason. Should the study be terminated prior to the completion of your participation, neither your doctor, nor the Presbyterian Hospital will be under any obligation to provide you with any drug used in the study after study termination. Your physician will work directly with you to decide upon further treatment after study termination.

COSTS

You will not receive any financial compensation for participating in this study. Laboratory tests (blood tests), x-rays, EKGs, and CT scans will be done at intervals to check the effects of the drug. These tests are felt to be part of good medical care and are covered by most types of insurance. You will be

responsible for any costs not covered by insurance. Possible costs will be discussed with you prior to the beginning of the study.

CONFIDENTIALITY

Information about you obtained during this study will be kept strictly confidential and never identified in any report or publication unless you sign a release. However, it is understood that you consent to the publication of study results so long as the information is anonymous and/or disguised so that identification cannot be made. Data collected during the study will comply with U.S. regulations, as applicable, and may be stored and analyzed by computer whether in the U.S. or abroad. If results of this study are reported in medical journals or at scientific meetings, identification of study participants is withheld. Also please note that agents of the Food and Drug Administration, and the Principal investigator may review your records.

VOLUNTARY PARTICIPATION

You are not obligated to participate in this investigational program or any other program in order to receive medical care for your disease. Participation in this study is voluntary. You are free to withdraw your consent to participate in this treatment program at any time without prejudice to your subsequent care. The Principal Investigator may discontinue this study treatment at anytime if it appears to be in your best interest. Declining to participate or withdrawing from participation will involve no penalty or loss of benefits to which you are otherwise entitled. You are free to seek care from a physician of your choice at any time. In the event you withdraw from participation in the study, your doctor may continue to follow you and follow-up clinical data may continue to be collected from your medical records.