A phase III, randomized controlled trial comparing Bevacizumab plus Fluorouracil (5-FU)/Leucovorin(LV) /radiation with 5-FU/LV/radiation alone in patients with locally advanced Pancreatic Cancer

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A. Study Purpose and Rationale

Pancreatic cancer continues to be one of the most lethal cancers. It is diagnosed in about 30,000 people in the United States each year and leads to about 30,000 deaths per year[1]. It has a grim prognosis because it is associated with early dissemination and resistance to current medical treatment. The only cure for pancreatic cancer is surgical resection, however only 15-20% of patients who present with pancreatic cancer have surgically resectable disease[2]. Even with surgery, the 5 year survival rate for resectable disease is only 20%. The majority of patients with pancreatic cancer present with unresectable disease (locally advanced) or metastatic disease. With the current standard treatment, median survival for patients with locally advanced and metastatic disease is 10 months and 5 months respectively[2]. Therefore, new systemic treatments that prevent spread and reverse progression of pancreatic cancer are critical.

Recently, a great deal of progress has been made in understanding the pathogenesis of pancreatic cancer. Studies have shown that pancreatic cancer overexpresses many growth factors and their receptors[2]. One of these growth factors, vascular endothelial growth factor (VEGF), a potent angiogenic stimulator, has been shown to promote endothelial cell proliferation in vitro and promote pancreatic cancer growth in vivo[3]. Further studies have looked at the association between VEGF expression and prognosis. Five out of six studies looking at either serum VEGF levels or VEGF expression in pancreatic cancer tissue samples from human subjects have shown that increased expression of VEGF is associated with cancer progression and decreased survival time[4,5,6,7,8,9]. Thus, therapy targeting VEGF may be effective in treating pancreatic cancer.

VEGF is expressed in a variety of other cancers including lung, breast, colon, renal, and ovarian carcinomas and therefore VEGF has been investigated as a target in cancer treatment[10]. In preclinical trials, a monoclonal antibody against VEGF was shown to inhibit the growth of human tumor xenografts in nude mice[11]. Anti-VEGF therapy has been successful for cancer treatment in humans as well. Bevacizumab is a monoclonal antibody to VEGF that was recently shown to be effective in metastatic colon cancer[12] and metastatic renal carcinoma[13]. In addition, encouraging preliminary data have been seen from a phase II trial using Bevacizumab in combination with gemcitabine in patients with metastatic pancreatic cancer[14].

Until now, Bevacizumab has not been used in the treatment of locally advanced, unresectable pancreatic cancer. Currently, the standard treatment for unresectable pancreatic cancer is fluoruracil-based chemoradiation. This treatment offers some symptomatic relief and a minor survival benefit, however the median life expectancy with this treatment is only about 40 weeks[2,15,16]. This trial will investigate the effect of standard treatment plus bevacizumab on survival in patients with locally advanced pancreatic cancer.

B. Study Design and Statistical Analysis

This will be a double-blinded, randomized, placebo-controlled trial investigating the effect of adding Bevacizumab to standard therapy in patients with locally advanced, unresectable pancreatic cancer. The primary outcome for this trial is overall survival. Forty-five subjects will be recruited for

each arm in the study in order to detect an increase in the median survival from 40 weeks to 52 weeks. The study size was determined using the unpaired t-test for a power of 80%, testing at p=0.05, and was based upon a standard deviation of 20 seen in previous studies[15,16].

Tumor response and progression of disease will be secondary outcomes. Tumor response will be measured by monthly CT scans. Progression of disease will be measured by evidence of metastases or tumor growth on monthly abdominal CT scans, decline in performance score of one or more levels, or loss of greater than 10% of pretreatment body weight.

C. Study Procedure

Following randomization, patients will receive 5-FU with leucovorin, radiation, plus bevazicumab or placebo. Patients will receive 6000 rads of radiation, administered in 3 two weeks courses of 200 rad/day for 5 days a week. Each course of radiation will be separated by two weeks. 5-FU will be administered in boluses of 500mg/m^2/day IV for 3 days at the beginning of each course of radiation. Four weeks following the completion of radiation, patients will receive weekly boluses of 5-FU at 500mg/m^2/day for up to two years from the beginning of treatment or until progression of disease. In addition, patients will receive 5mg/kg IV of bevacizumab (or placebo) every two weeks for 2 years or until progression of disease. The sequence of treatment for the subjects is seen in the following table:

Week	Radiation	5-FU/LV*	Bevacizumab/ placebo
1	200rad/day x5d	500mg/m^2 x3days	5mg/kg
2	200rad/day x5d		
3	Off		5mg/kg
4	Off		
5	200rad/day x5d	500mg/m^2 x3days	5mg/kg
6	200rad/day x5d		
7	Off		5mg/kg
8	Off		
9	200rad/day x5d	500mg/m^2 x3days	5mg/kg
10	200rad/day x5d		
11	Off		5mg/kg
12	Off		
13	Off		5mg/kg
14	Off		
15	Off	500mg/m^2 x1d	5mg/kg
16	Off	500mg/m^2 x1d	
		Continues weekly x2years	Continues q2weeks x2 years

*Leucovorin will be given in doses of 20mg/m^2 on the first day of each cycle of 5-FU.

Patients will be re-evaluated monthly by physical exam, laboratory tests (Chem7, LFTs, CBC, urinalysis), and CT scans for the first two years of the study and then every three months. Adverse events will be monitored based upon patient reports, physical exams and laboratory tests.

A Data and Safety Monitoring Board made up of three colleagues from another institution who are unblinded to the treatment assignments of participants will monitor adverse reactions that occur throughout the study. The study will be discontinued if a greater than expected number of adverse events occur in the treatment group.

D. Study Drugs

Bevacizumab (Avastin) is FDA approved for use in metastatic colorectal cancer. Studies have shown that it is also effective in metastatic renal cell carcinoma[13]. Preliminary results using bevacizumab in metastatic pancreatic cancer are encouraging[14]. In phase I trials, bevacizumab did not have dose-limiting toxicity at doses ranging from 0.1 to 10mg/kg and bevacizumab was safely administered in combination with 5-FU/leukovorin[17, 18]. There is currently a phase I trial taking place looking at bevacizumab in combination with chemoradiation in pancreatic cancer[19]. This trial will provide data regarding the safety of administration of bevazicumab in combination with radiation and will determine whether this proposed phase III study can be carried out. In addition, prior to carrying out this phase III trial, a phase II trial involving a smaller number of subjects must be complete in order to further evaluate the toxicity of the chemoradiation combination proposed here.

Bevacizumab will be administered intravenously at a dose of 5mg/kg every two weeks. This was the dose and administration schedule found most effective in metastatic colorectal cancer[12].

The known adverse events associated with bevacizumab are as follows:

1. Most serious adverse events:
    a. GI perforation (3-4%)
    b. Wound dehiscence (1%) – in patients who had not undergone surgery within 28 days of starting the therapy
    c. Hemoptosis – occurred only in patients with lung cancer
2. Most common severe adverse events (grade 3 or 4)
    d. Asthenia (grade 3 or 4)
    e. Pain (grade 3 or 4)
    f. Hypertension (grade 3)
    g. Diarrhea (grade 3 or 4)
    h. Leucopenia (grade 3 or 4)
3. Most common adverse events of any severity: asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria.

E. Medical Device

Not applicable

F. Study Questionnaires

Not applicable

G. Study Subjects

Participants will be patients aged 20–75 years of age with locally advanced pancreatic adenocarcinoma confirmed by biopsy. Staging will be done by CT or MRI and patients with unresectable disease, due to encasement of vasculature by the tumor or association of bulky peripancreatic lymphadenopathy, will be included in this study. Patients must have an ECOG performance status 0-2 to be enrolled in this study. Exclusion criteria for this study includes evidence of metastases, previous radiation therapy or chemotherapy, coexistence of an active neoplasm, blood pressure >160/90, history of vascular disease, concurrent anticoagulation therapy, urinary excretion of greater than 500mg protein per day, and surgery within 4 weeks of initiation of the study treatment.

H. Recruitment of Subjects

Patients presenting to CPMC with newly diagnosed locally advanced pancreatic cancer who meet the eligibility criteria will be recruited for this study.

I. Confidentiality of Study Data

Information obtained about patients during this study will be kept strictly confidential. Each participant will be assigned a unique code number to keep track of their data and therefore no personal identifiers will be present on study data. Data collected will be accessible only to the investigators.

J. Potential Conflict of Interest

There is no conflict of interest. None of the investigators in this study have a proprietary interest in the drug being investigated.

K. Location of the Study

This study will take place at the chemotherapy and radiation oncology treatment centers at CPMC.

L. Potential risks

A potential risk to participants in this study is experiencing one or more of the adverse events associated with bevacizumab that are listed in section D. Participants are also at risk of experiencing an adverse event associated with bevacizumab that has not been discovered yet due to the relatively small number of patients who have received the drug. Participants will be unaware of whether they are receiving bevacizumab or placebo during the study and therefore may be at risk of experiencing a worse outcome if bevacizumab does turn out to be effective in this disease.

M. Potential benefits

There is reasonable evidence to suggest that bevacizumab will be effective in the treatment of pancreatic cancer and therefore patients in the treatment arm of this study may benefit. In general, the effect of bevacizumab on pancreatic cancer is unknown and therefore participants in this study may or may not benefit.

N. Alternative Therapies

Patients who choose not to enroll in this study have the option of either receiving no treatment, receiving the standard treatment, or receiving the treatment offered in another trial where the efficacy is unknown (as in this trial).

O. Compensation to subjects

There will be no compensation to subjects for participating in this study.

P. Costs to subjects

There will be no additional costs to the subjects as a result of participating in this study.

Q. Minors as Research Subjects

There will be no minors enrolled in this study.

R. Radiation or Radiactive Substances

Patients will receive radiation therapy based upon the standard protocol for patients with locally advanced pancreatic cancer. Approval will be obtained from the Joint Radiation Safety Committee prior to the start of this study.

S. References

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