Primary prevention of thromboembolism in pancreatic cancer patients undergoing chemotherapy using a low-molecular weight heparin.

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Lay Abstract:

Venous thromboembolism (VTE) is a condition in which blood clots form in the deep veins of the extremities. One complication of VTE is pulmonary embolism (PE), or migration of the clot into the blood vessels that supply the lungs and can result in death.

One group of patients known to be at higher risk of VTE is cancer patients. Among these, patients with pancreatic cancer are at particularly high risk, with 20% developing VTE in the first year after diagnosis. Another risk factor associated with VTE is chemotherapy, which is often given to pancreatic cancer patients and puts them at additional risk. While progression of disease is the most common cause of death in these patients, VTE and its complications are thought to be the second most common cause of death.

Low-molecular weight heparin (LMWH) is a medication administered as a daily injection into the skin. Heparin aids in preventing the development of blood clots. It is widely used to prevent VTE in patients who have previously had VTE, and in patients who are undergoing surgery. However it is not known whether heparin treatment will be effective in decreasing the incidence of VTE in patients with pancreatic cancer. Some concerns with heparin treatment in this group are that these patients may be at a higher risk for bleeding complications, both due to their burden of gastrointestinal disease and due to low platelet counts as a consequence of chemotherapy. The magnitude of bleeding risk with heparin treatment is also not known in these patients.

We propose to conduct a study in which one group of 200 patients will be randomly assigned to undergo chemotherapy for pancreatic cancer with once daily injections of low-molecular weight heparin, and another group of 200 patients will be randomly assigned to undergo chemotherapy without heparin. Throughout the one-year study, patients will be assessed for the incidence of VTE. Other outcomes that will be evaluated in the study are the number of bleeding events and mortality.

A. Study Purpose and Rationale

Malignancy has long been associated with thromboembolic disease. Estimates of the incidence of venous thromboembolism (VTE) in cancer patients vary widely in the current literature; this variability may be partly because a diagnosis of cancer encompasses a diverse population of patients with varying disease pathology, stage, and severity. While one large population-based study cited a rate of 1.6% over two years (1), others have found a rate of 12% over 8 months in a population of oncology outpatients (2), and 7.8% over 2 years in a similar population (3). Despite these differences in absolute risk in studies of cancer patients, there are several subgroups that have been consistently shown to be at high risk. These include patients with prior VTE, who are two to three times more likely than non-cancer counterparts to suffer a second VTE (4, 5). Further risk factors include the tumor type: lung, colon and prostate are the most common due to the prevalence of these diseases; however ovary, brain, and pancreatic cancer, and lymphoma have the highest risk relative to incidence (6).

Patients with pancreatic cancer have a profoundly elevated risk of VTE. A retrospective study of the California Cancer Registry found that in 2933 pancreatic cancer patients with metastatic disease, the rate of VTE over the first patient-year after diagnosis was 20% (1). Autopsy studies cite a 50% prevalence of venous thromboembolism in those with pancreatic cancer (7). Factors that modulate the risk of thrombosis include the presence of metastatic disease, surgery, chemotherapy, and the placement of a central venous catheter. A prospective study of 202 pancreatic cancer patients found that chemotherapy increased the rate of venous thrombosis by a factor of 4.5 (8), however in other studies estimates have been closer to 2 (9, 10). Not only does VTE cause significant morbidity in this patient population, it is also thought to be the second most common cause of death, though progression of disease is by far the most common (11).

Though studies have examined different pharmacologic therapies for secondary prevention of VTE in patients with cancer, primary prevention studies are currently lacking in the literature. The two primary prevention studies in the literature have focused on patients at high risk. One study examined the incidence of VTE in a group of stage IV breast cancer patients undergoing chemotherapy (12). This study showed that low-dose coumadin to a target INR of 1.3-1.9 was effective in reducing the risk of VTE and did not increase the risk of major bleeding. Though prophylactic anticoagulation has been shown to be beneficial in this particular group, no general guidelines are in place for when to prescribe anticoagulants, and a survey among oncologists have found that though the perception of risk is high, prescribing practices vary considerably (13).

We propose a study in which patients with a diagnosis of pancreatic adenocarcinoma undergoing chemotherapy will be randomized to either heparin or no anticoagulation for primary prevention of VTE. We hypothesize that pharmacologic anticoagulation during chemotherapy for pancreatic cancer will reduce the incidence of venous thrombosis and pulmonary embolism in the treatment group.

B. Study Design and Statistical Analysis

Medical centers and oncology practices will be the primary source of patient recruitment. Patients will be recruited at the time of initiation of chemotherapy for

pancreatic cancer, and assigned to low-molecular weight heparin at prophylactic doses, or no injections. Patients will not be blinded, as placebo injections introduce an unacceptable level of pain and discomfort to this group of patients with likely terminal illness. Discontinuation of the drug will be permitted for major bleeding, for minor bleeding which is deemed intolerable by the patient, and for new-onset renal failure which represents a contraindication to administration of the drug.

The goal for patient enrollment will be 468 patients per arm. This calculation is based on a 20% incidence of VTE in the first year after diagnosis, at an alpha of 0.05, powered to detect a reduction in the primary endpoint (thromboembolic disease as evidenced by DVT and/or PE) from 20% to 13%, which represents a 35% reduction. Secondary endpoints will include death, and major bleeding defined as a fall in hemoglobin by 2g/dL or retroperitoneal/intracranial bleeding.

The primary analysis will be a chi-squared test on proportions and based on intention-to-treat. Kaplan-Meier curves will be generated to document event-free survival.

The secondary analysis will utilize the Cox-proportional hazard model based on the following patient characteristics: stage of cancer at time of entry into the trial, ECOG performance status, type of chemotherapy given, presence of central venous catheter, and radiation therapy.

C. Study Procedure

Patients will be recruited when initiating chemotherapy for pancreatic cancer stage II or above. Informed consent will be obtained from each patient. Patients will be seen or contacted by a study physician every three months and assessed for any of the outcome measures. They or a family member will be taught how to administer subcutaneous injections of LMWH, which they will continue for the duration of chemotherapy and for one month thereafter. On entry into the study, they will also be educated on the presenting signs and symptoms of VTE and PE and will be instructed to report these symptoms to their doctor. They will also be educated on the signs and symptoms of bleeding. A diagnosis of PE will be confirmed with computed tomographic angiography (CTA) or a high-probability ventilation-perfusion scan. A diagnosis of DVT will be confirmed with duplex ultrasonography, computed tomographic venography or magnetic resonance venography. A radiologist blinded to the patient randomization and unaffiliated with the investigators will confirm the diagnosis in each case. Patients will be followed for one year or until death.

D. Study Drugs

Lovenox® is a drug belonging to the class of low-molecular weight heparins (LMWH). Heparin is composed of mucopolysaccharides of varying molecular weights whose overall effect is to inhibit factor Xa and enhance inhibition of clotting through antithrombin III. Low molecular weight heparins are fractionated and have a greater effect on factor Xa than standard heparin. The anticoagulant effects of LMWH have been extensively studied; they have been found to be effective for DVT prophylaxis in immobilized patients with acute medical illness, and in patients undergoing surgery.

Class I recommendations are in place for these indications. The prophylactic dose for VTE prevention is 40mg administered as subcutaneous injection daily.

Contraindications to heparin therapy include active bleeding, severe thrombocytopenia, or a history of heparin-induced thrombocytopenia. Situations in which heparin should be used with caution include liver disease with impaired hemostasis, gastrointestinal ulcer, hereditary bleeding disorders, hypersensitivity to heparin products, or renal dysfunction with a creatinine clearance <30mL/minute.

E. Study Subjects

Patients aged 18-70 with a diagnosis of pancreatic cancer stage II or above and undergoing chemotherapy will be eligible for enrollment in this trial. Patients who have had a previous VTE may be included if they are on no prophylaxis at the time of enrollment. Patients with the following contraindications to heparin therapy will be excluded: hypersensitivity to heparin, a history of heparin-induced thrombocytopenia, platelets <50,000/mm^3, gastrointestinal bleeding in the past 12 months, coagulopathy evidenced by prolonged PT/aPTT, or brain metastases. Additionally patients with an estimated survival of less than 3 months or an ECOG performance status >3 will be excluded. All patients must be capable of providing informed consent.

F. Recruitment of Subjects

Patients will be recruited by investigators at participating medical centers and at oncology practices affiliated with those medical centers.

G. Confidentiality

Patients will be identified by a unique number which will be associated with their name in a locked location by the primary investigator at each site. Patient data will be associated with the identifying number in all analyses, and the patients will never be identified by name in reports.

H. Potential Risks

Potential risks to the patients participating in this study include major bleeding including gastrointestinal bleeding, intracranial bleeding, and retroperitoneal bleeding. The risk of these complications is low in patients without pancreatic cancer, with an incidence of 0.3% (14). Patients with pancreatic cancer may be at higher risk, though those with prior gastrointestinal bleeding who are presumed to be at higher risk will be excluded from the study. Minor bleeding events may include injection site bruising, hematuria, and epistaxis. There is a small risk of heparin-induced thrombocytopenia with most incidence estimates being <1%. The incidence of heparin-induced thrombocytopenia with thrombosis is even lower. Patients who meet diagnostic criteria for HIT will have therapy discontinued and a HIT antibody test sent.

I. Potential Benefits

The study subjects may or may not benefit from participation in this study. If heparin for DVT and PE prophylaxis is found to be efficacious in preventing the morbidity associated with these conditions, or found to prolong survival, the patients in the treatment arm will benefit from participation in the study.

This study will benefit society in that it will define whether treatment with LMWH can prevent VTE as a complication of pancreatic cancer. As very little is known about the risks and benefits of LMWH in these patients, the study results will be important in defining future standards of care for this group.

J. Compensation

Patients will be compensated for travel expenses related to follow-up visits.

K. References

1) Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Archives of Internal Medicine 2006; 166:458-64.

2) Sallah S, Wan JY, Nguyen NP. Venous thrombosis in patients with solid tumors: determination of frequency and characteristics. Thrombosis and Haemostasis 2002; 87:575-9

3) Kroger K, Weiland D, Ose C, Neumann N, Weiss S, Hirsch C, Urbanski K, Seeber S, Scheulen ME. Risk factors for venous thromboembolic events in cancer patients. Annals of Oncology 2006; 17:297-303

4) Prandoni P. Cancer and thromboembolic disease: how important is the risk of thrombosis? Cancer Treatment Reviews 2002; 28:133-136.

5) Levitan N, Dowlati A, Remick SC. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy: risk analysis using Medicare claims data. Medicine 1999;78:285–291.

6) Stein PD, Beemath A, Meyers F, Ekaf E, Sanchez J, Olson RE. Incidence of venous thromboembolism in patients hospitalized with cancer. The American Journal of Medicine 2006; 119:60-68

7) Khorana AA, Fine RL. Pancreatic cancer and thromboembolic disease. Lancet Oncology 2004; 5(11):655-63.

8) Blom JW, Osanto S, Rosendaal FR. High risk of venous thrombosis in patients with pancreatic cancer: a cohort study of 202 patients. European Journal of Cancer 2006; 42(3):410-414.

9) Blom JW, Vandoschoot JP, Oostindier MJ, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. Journal of Thrombosis and Haemostasis 2006; 4(3):529-35.

10) Khorana AA, Francis CW, Culakova E, Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer 2005; 104(12):2825-9

11) Neoptolemos JP, Dunn JA, Stocken DD. Adjuvant chemoradiotherapy and chemotherapy in respectable pancreatic cancer: a randomized controlled trial. Lancet 2001; 358:1576-85.

12) Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanga A, Samosh M, Bramwell V, Pritchard KI, Stewart D, Goodwin P. Double blind randomized trial of very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. The Lancet 1994; 343:886-9.

13) Kakkar AK, Levine M, Pinedo HM, Wolff R, Wong J. Venous thrombosis in cancer patients: insights from the FRONTLINE survey. Oncologist 2003; 8(4):381-8.

14) Leonardi MJ, McGory ML, Ko CY. The rate of bleeding complications after pharmacologic deep venous thrombosis prophylaxis: a systematic review of 33 randomized controlled trials