Exocrine Pancreas Cancer and Thromboembolic Events: A Systematic Literature Review

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Abstract

Exocrine pancreas cancer continues to represent a significant therapeutic challenge, with high rates of mortality and morbidity, including from thromboembolic events, which have long been described as a frequent complication of the disease. This article provides a systematic and comprehensive review of the literature to address the clinical and pathologic features recognized in pancreas cancer pertaining to thrombosis, and to discuss ongoing investigations of prophylactic anticoagulation in the hopes of improving disease-related outcomes. (*JNCCN* 2012;10:835–846)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Distinguish risk factors for thromboembolism among patients with pancreatic cancer
- Analyze recommendations for primary prophylaxis against thromboembolism among patients with pancreatic cancer
- Assess the best treatment for thromboembolism among patients with pancreatic cancer
- Evaluate outcomes improved with treatment of thromboembolism among patients with pancreatic cancer

Malignancy is a well-established risk factor for the development of venous thromboembolic events, both in hospitalized and ambulatory patients. Venous thromboembolic events are a major contributor to cancer- and treatment-related morbidity and mortality. Exocrine pancreas cancer is one of the most common malignancies associated with thrombosis, with most modern studies reporting incidence ranging from 5% to 27%.^{1–6}

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Various patient-, treatment-, and increasingly recognized pancreas tumor-related factors contribute to thrombosis (Table 1). Additionally, venous thromboembolic events have been found to portend a poorer prognosis in patients with pancreas cancer,³ and have been implicated in early deaths after diagnosis.⁷ Patients with various cancers diagnosed within 1 year of a thrombosis often have more extensive malignancy and worse outcome.⁸ This association between thrombosis and shorter survival has been validated in a prospective case-control study by Mandala et al.⁹ Anticoagulants may have treatment effects on the malignancy.^{10,11}

Pancreas cancer is notoriously difficult to treat, and current chemotherapy regimens offer only modest disease control. Therefore, new therapies are clearly needed in hopes of impacting survival and treatment- and disease-related morbidity, including that from thrombosis. Although both superficial thrombophlebitis and arterial thromboses, such as myocardial infarction and stroke, have been well described in pancreas cancer, this article focuses on deep venous thromboses (hereafter referred to as

thrombosis), because these predominate. The clinical and molecular underpinnings of thrombosis in patients with cancer are first discussed, highlighting key studies performed not only in pancreas cancer but also in other tumor types.

Methods

After an initial query of PubMed for literature on pancreas cancer and thrombosis, and in collaboration with the authors' institution's library staff, a comprehensive search was performed of articles contained in 5 databases (PubMed, Embase, Web of Science/ Science Citation Index, Scopus, and Cochrane) involving the key words (and associated subterms) *pancreas cancer*, *anticoagulation*, and *thrombosis*. From a search yield of 1895 results, articles chosen for inclusion herein predominantly consisted of original studies on preclinical pathophysiology or clinical trials regarding thrombosis primary or secondary prophylaxis in patients with pancreas cancer. Articles outside of this purview were excluded.

Patient-Related Risk Factors for Thrombosis

The 1860s saw the description of Virchow's triad and the first association between thrombosis and malignancy by Trousseau.¹² Since then, numerous clinical variables have been shown to either contribute to or be associated with thrombogenicity, and many have been studied in the cancer population, specifically in patients with pancreas cancer. Prediction tools have been created for the risk assessment and stratification of patients undergoing cancer treatment.¹³⁻¹⁶ Khorana et al.¹⁴ developed and validated their model, which showed an association between thrombosis and the following 5 clinical factors: cancer site (for which pancreas was deemed a very high-risk site); platelet count 350,000/L or greater; hemoglobin less than 10 g/dL (and/or use of erythropoietin-stimulating agents); leukocyte count greater than 11,000/L; and body mass index of 35 kg/m² or greater. Ay et al.¹⁷ used these factors and also incorporated the biomarkers soluble P-selectin and D-dimer.

Thrombosis in cancer has also been explored outside of the above prediction models, including in hospitalized patients with neutropenia.¹⁸ Analysis of the Vienna Cancer and Thrombosis Study, published in

Table 1 Selected Factors Relevant to Pancreas Cancer and Thrombosis

Molecular Associations

- Tissue factor^{36,42}
- Thrombomodulin³⁴
- Thrombin³⁵
- Thrombin-antithrombin III complex³⁶
- Plasminogen activator inhibitor-1³⁷
- Platelet factor 4³⁸
- Fibrin⁴⁰
- Tissue factor pathway inhibitor⁴¹

Clinical and Treatment Variables

- Hospitalization/sedentary status
- Surgery
- Venous access/catheterization
- Weight extremes^{14,21}
- Blood type group A²²
- Leukocytosis^{13,14}
- Anemia^{13,14}
- Thrombocytosis^{13,14}
- Medications (erythropoietin-stimulating agents,^{13,14} chemotherapy,³¹⁻³³ megestrol⁸⁶)
- Comorbidities (heart, liver, and kidney disease; diabetes)

2010, illustrated high platelet count as an independent predictor of thrombosis,¹⁹ a correlation originally noted by Khorana et al.¹⁴ A recent abstract²⁰ showed that albumin level may independently predict for the development of thrombosis. Finally, patient weight, particularly obesity, has also been studied and identified to be a potential risk factor for thrombosis in patients with cancer. In pancreas cancer, Greenblatt et al.²¹ recently showed that both underweight and obesity were associated with more venous thrombosis and worse overall survival after pancreas resection.

An interesting clinical observation regarding thrombosis risk specifically in pancreas cancer relates to blood type. In a retrospective review of institutionally treated patients with pancreas cancer, thromboses were significantly more common not only in patients with metastatic disease but also in those with A versus non-A blood type (odds ratio [OR], 3.0; 95% CI, 1.4–6.6; $P = .005$).²²

Molecular Risk Factors for Thrombosis

The molecular underpinnings of thrombosis in malignancy have been extensively investigated. The myriad details of this relationship are beyond the scope of this review (although explored more fully in the “Pancreas-Specific Molecular Risk Factors for Thrombosis” section), but key components include tumor cell interactions with endothelium, platelets, and leukocytes; cytokine release; and the dual upregulation of procoagulant molecules along with downregulation of anticoagulant molecules. Investigations of molecular predictors for thrombosis have been performed recently and included patients with pancreas cancer. The Vienna Cancer and Thrombosis Study prospectively analyzed factors associated with the risk of thrombosis in 821 patients with various newly diagnosed malignancies or with disease progression and not actively undergoing treatment.²³ Elevated levels of D-dimer and prothrombin fragment 1 and 2 were independent predictors for the development of thrombosis. The same group also prospectively showed soluble P-selectin to be an independent predictor of thrombosis.²⁴ Finally, the group also found that thrombin generation increased the risk of venous thrombosis.²⁵

Treatment-Related Risk Factors for Thrombosis

Associations between thrombosis and various treatments, including surgery, central venous catheters, and hospitalization, are well documented in the medical literature.^{26–28} Erythropoietin-stimulating agent use has declined sharply in the past few years given the growing knowledge about thrombogenicity and worsened survival.^{29,30} Chemotherapy in pancreas cancer also increases thrombogenicity, including the commonly used agent gemcitabine.^{31,32} Thrombosis occurred in 18.1% of 932 patients with various malignancies treated with a cisplatin-containing regimen in 2008 at Memorial Sloan-Kettering Cancer Center.³³ The most common cancer associated with thrombosis was pancreas cancer (representing 8.5% of the cohort), which occurred in 36.7% of the patients.

Pancreas-Specific Molecular Risk Factors for Thrombosis

Investigators have shown the interaction between many procoagulant and fibrinolysis molecules and the development and activity of pancreas cancer, both in cell lines and in vivo. These observations underlie the notion that prophylactic anticoagulation in patients with pancreas cancer may exert a therapeutic benefit. These molecules include thrombomodulin,³⁴ thrombin,³⁵ thrombin-antithrombin III complex,³⁶ plasminogen activator inhibitor-1,³⁷ platelet factor 4,³⁸ P-selectin glycoprotein ligand 1,³⁹ fibrin,⁴⁰ and tissue factor pathway inhibitor,⁴¹ with the most attention focused on the role of tissue factor⁴² (both soluble and cell membrane-bound³⁶) in pancreas carcinogenesis, and related thrombogenicity. Delluc et al.⁴³ observed higher levels of tissue factor in patients with pancreas cancer and thrombosis than in those with non-pancreas cancers and thrombosis or with idiopathic thrombosis.

Tissue factor has also been shown to enable procoagulant activity through microparticles released from cells both in vivo and in vitro,⁴⁴ including in a pancreas cancer cell line,⁴⁵ and these tissue factor-bearing microparticles have been shown to be present in higher amounts in patients with thrombosis and cancer than in those with idiopathic thrombosis without cancer or those with cancer without thrombosis.⁴⁶

Anticoagulation in Solid Malignancies

Numerous anticoagulation trials have been conducted in solid malignancies, with a survival benefit suggested in several trials, especially in patients with limited-stage small cell lung cancer with no history of thrombosis.⁴⁷ The suggestion of possible benefit of anticoagulation in the survival outcome of patients with cancer stems from both primary and secondary prophylaxis trials. Numerous secondary prophylaxis studies have been conducted wherein patient outcomes are analyzed in subgroups of the larger trial population. Moreover, primary end points in these trials address thrombosis-specific factors, such as thrombosis recurrence, whereas survival-related outcomes serve as secondary end points. With these caveats in mind, randomized controlled trials and meta-analyses of these trials have reported survival benefits in cancer patients randomized to low-molecular-weight heparin compared with vitamin K antagonists and unfractionated heparin. Low-molecular-weight heparin has been postulated to directly influence tumor growth, angiogenesis, and metastasis, which are effects thought not to be exerted by vitamin K antagonists or unfractionated heparin.

One of the most noted secondary thromboprophylaxis randomized controlled trials compared thrombosis treatment with 6 months of dalteparin versus a vitamin K antagonist.⁴⁸ The primary end point was recurrent venous thrombosis, which occurred significantly less in patients receiving dalteparin. Although no difference in survival was seen between the treatment arms, a post hoc subgroup analysis of the patients with localized cancer yielded a 12-month all-cause mortality of 35% in the vitamin K antagonist group versus 20% in the dalteparin group ($P = 0.04$). In patients with metastatic cancer, no survival difference was reported (69% and 72%, respectively, for patients with a vitamin K antagonist and dalteparin; $P = .46$).⁴⁹ Compared with unfractionated heparin, meta-analyses suggest survival improvements in patients treated with low-molecular-weight heparin.^{50–53}

Regarding primary thromboprophylaxis, small cell lung cancer has been perhaps the most extensively studied solid tumor type,^{54–58} and in some of these trials, a statistically significant benefit in time to progression and/or survival with anticoagulation has been seen in these patients, including with warfarin,⁵⁴ unfractionated heparin,⁵⁶ and low-molecular-

weight heparin.⁵⁸ In the low-molecular-weight heparin and unfractionated heparin trials, the benefit was more pronounced in patients with limited-stage disease, but was also statistically significant in patients with advanced small cell lung cancer. These trials should, however, be interpreted in the context of limited sample sizes, incompletely reported complication and performance status data, heterogeneous patient populations, and varying anticoagulant doses.

The results of more recent primary thromboprophylaxis controlled trials of low-molecular-weight heparin in non-small cell lung cancer tumor types have been mixed.^{59–61} Several meta-analyses have set out to clarify the degree of anticoagulant effect on patient survival, although details of these trials^{62–64} are outside the scope of this review.

Further randomized controlled trials are needed to clarify this possible antineoplastic benefit, which also must be weighed against cost and bleeding risk before anticoagulants are routinely implemented for primary prophylaxis.^{63,65} Alternatives to conventional anticoagulants are also deserving of further investigation. One trial (ClinicalTrials.gov identifier: NCT01020006) is currently investigating a factor VIIa inhibitor in patients with advanced pancreas cancer. Additionally, statin use has been associated with lower thrombosis risk in retrospective studies,^{66,67} possibly because of lipid-mediated platelet activation and endothelial disruption.

Incidence and Effect of Thrombosis in Pancreas Cancer

Sproul⁶⁸ has been credited with first fully describing the association of thrombosis and pancreas cancer in 1938, reporting a frequency of 30% in a large consecutive autopsy series of 4258 cases (of which 47 patients had pancreas cancer). Since then, multiple reports have followed, firmly establishing this observation. Table 2 details these pancreas cancer-specific cohorts. Autopsy series of pancreas cancer, in particular, have consistently shown the commonality of thrombosis (pulmonary embolism specifically in one study⁶⁹: 42%), ranging from 19% to 67% of all cases.^{70–74} In recent decades, far fewer reports use autopsy methodology, and instead describe the incidence of thrombosis diagnosis in living patients clinically. Worldwide, a Dutch center examined thrombosis rates in 202 patients with pancreas cancer from 1990 to 2000,¹ showing a more than

Table 2 Incidence of Thrombosis in Pancreas Cancer–Specific Cohorts

Reference	N	Study Type	% ^a	Notes
Cubilla and Fitzgerald, ² 1978	380	Retrospective	14	Histologically confirmed patients at MSKCC ^b from 1949–1972
Pinzon et al., ⁵ 1986	130	Retrospective	6.9	Consecutive patients at MDACC; mucin production and body/tail location associated with thrombosis
Mandala et al., ³ 2007	227	Retrospective	26	Patients with unresectable pancreas cancer in 3 clinical trials
Mitry et al., ⁶ 2007	90	Retrospective	27	No survival differences between patients with and without thrombosis
Oh et al., ⁴ 2008	75	Retrospective	5	Korean authors suggest possible ethnobiologic factors in relatively low incidence
Epstein et al., ⁷⁵ 2011	1915	Retrospective	36	Patients with pancreas cancer at MSKCC receiving chemotherapy
Mikal et al., ⁷⁰ 1950	100	Autopsy series	67	18% in head of pancreas, 49% in body/tail
Thompson et al., ⁷¹ 1952	157	Autopsy series	31	25 single thromboses, 23 patients with multiple thromboses
Soederstroem and Bjersing, ⁷² 1963	50	Autopsy series	52	Included anatomy: inferior vena cava, pelvic and thigh veins
Lowe and Palmer, ⁷⁴ 1967	100	Autopsy series	29	8% clinical, 21% autopsy
Mao et al., ⁷³ 1995	154	Autopsy series	19.4	Consecutive autopsies at 3 affiliated Ohio teaching hospitals
Blom et al., ¹ 2006	202	Prospective	108.3 ^b	Increased risk with body/tail tumors, chemotherapy, surgery, and metastatic disease

Abbreviations: MDACC, MD Anderson Cancer Center; MSKCC, Memorial Sloan-Kettering Cancer Center.

^aPercentage incidence figures are relative to the individual specific study periods.

^bIn 1000 patient years.

50-fold increase compared with the general population. The most recently reported single-institution review actually reported a relatively low thrombosis incidence of 5% in 75 Korean patients with pancreas cancer, suggesting a possible ethnicity effect.⁴

At Memorial Sloan-Kettering Cancer Center, in 1915 patients receiving chemotherapy from January 1, 2000, through December 31, 2009, 36% had been diagnosis-coded with a thrombosis and confirmed by chart review.⁷⁵ The investigators found that thrombosis was correlated with significantly worse overall survival in these patients (hazard ratio [HR], 2.6; 95% CI, 2.3–2.8; $P < .01$), particularly early thromboses (HR, 2.1; 95% CI, 1.7–2.5; $P < .01$ vs. late or no thrombosis). Early thromboses were defined as those diagnosed before, or up to 1.5 months after, a pancreas cancer diagnosis. The interaction between any thrombosis and survival outcome in pancreas cancer was shown in a previous report on 227 patients with advanced disease.³ However, a more recent retrospective review of 201 patients with pancreas cancer reported no statis-

tical difference in survival between patients with and without thromboses ($P = .9$).⁷⁶ Moreover, the effect of early thrombosis timing on pancreas cancer–specific survival has never been reported.

Anticoagulation in Pancreas Cancer

Given the urgent need for improvements in pancreas cancer therapeutics, studies have been performed examining the role of primary thromboprophylaxis. Investigations reported thus far, some only at an early analysis time point⁷⁷ and not all solely in patients with pancreas cancer,⁷⁸ show a reduction in thromboembolic events,⁷⁹ and some even suggest improvements in time to progression and overall survival.^{80,81} However, a more recent trial, albeit also not solely in patients with pancreas cancer, did not show a difference in time to progression or overall survival.⁸²

Although the use of newer-generation heparins has recently been reported in the adult oncology setting, and despite the fact that oral anticoagulants

(e.g., direct thrombin inhibitors and factor Xa inhibitors) have actively been studied recently in the non-cancer population, a strong foundation of evidence nevertheless supports low-molecular-weight heparin over vitamin K antagonists in the initial and long-term management of thrombosis in patients with cancer.⁸³ Therefore, recent anticoagulation studies in the pancreas cancer population primarily use low-molecular-weight heparin. Most studies have evaluated symptomatic peripheral thromboses, although a retrospective study by Price et al.⁸⁴ of patients with pancreas cancer with portal vein thromboses suggested that survival may be increased with anticoagulation. These results must be interpreted in the context of the study's retrospective design and the lack of randomized trials of anticoagulation for portal vein thromboses. For portal vein thromboses, individual patient factors must be taken into account, such as acuity of the event, bleeding risk, and presence of underlying liver disease.

The following sections discuss trials involving anticoagulants in pancreas cancer. Methodology, anticoagulant, and tumor type are key differences to be noted across these investigations. Table 3 includes pancreas cancer-specific randomized trials, including those with results yet to be reported.

Retrospective Studies

A German group reported provocative results in a retrospective analysis of 240 patients with advanced pancreas adenocarcinoma treated with chemotherapy.⁸¹ Of the 213 patients on whom documentation was available, 94 had received low-molecular-weight heparin (specific doses were not indicated; patients either received prophylactic-dose certoparin [$n = 39$], prophylactic-dose dalteparin [$n = 50$], or therapeutic dose nadroparin [$n = 5$]). Overall survival was measured as time from initiation of chemotherapy to death and was found to not vary significantly, depending on whether low-molecular-weight heparin was administered. However, when dividing their population into metastatic and locally advanced pancreas cancer, the investigators observed a statistically significant effect of low-molecular-weight heparin on the survival of patients with metastatic disease (6.6 and 3.8 months, respectively, for the low-molecular-weight heparin group and the non-low-molecular-weight heparin group; HR, 0.6; 95% CI, 0.4–0.8; $P = .006$). As the authors conclude, this retrospective analysis requires prospective validation.

Prospective, Nonrandomized Studies

A Turkish group examined a similar question in a prospective, albeit nonrandomized design.⁸⁰ They treated 69 patients with advanced pancreas cancer with a combination of gemcitabine and cisplatin with ($n = 35$) or without ($n = 34$) the addition of the low-molecular-weight heparin nadroparin (2850 IU/d). Patients who received low-molecular-weight heparin did so in the context of prospective evaluation, whereas the group receiving chemotherapy alone were patients previously treated with the same regimen, and their outcomes were analyzed retrospectively. Patients were matched equally in terms of extent of disease. The nadroparin group had longer time to progression and overall survival compared with the chemotherapy-alone group (7.3 vs. 4.0 months; $P = .0001$; 13.0 vs. 5.5 months; $P = .0001$). Toxicity was similar in both groups, and specifically no treatment-related bleeding complications were seen in the nadroparin group. No statistically significant difference in thrombosis was seen between the groups, suggesting an alternate mechanism for low-molecular-weight heparin benefit. Nonetheless, these results must be considered in the context of the nonrandomized study design and small sample size.

Although the above investigations used low-molecular-weight heparin primary prophylaxis, low-dose (1.25 mg/d) warfarin has been tested by Nakchbandi et al.⁸⁵ Their sample size of 17 patients was very small, however. This and other methodologic concerns limit the applicability of warfarin as a therapeutic strategy in this setting.

Prospective, Randomized Studies (Not Pancreas Cancer-Specific)

Agnelli et al.⁷⁸ published a randomized placebo-controlled trial of nadroparin for primary thromboprophylaxis in patients of broad solid tumor types receiving systemic chemotherapy for advanced disease. In a 2:1 ratio, the patients included in the analyses received nadroparin ($n = 769$) or placebo ($n = 381$) for the duration of chemotherapy, up to a maximum of 4 months. The study's primary end point was symptomatic venous or arterial thromboembolic events. Of the patients in the nadroparin arm, 2.0% versus 3.9% treated with placebo experienced a thromboembolic event ($P = .02$). No significant difference in major or minor bleeding episodes was seen between the arms. van Doormaal et al.⁸² also investigated primary prophylaxis nadroparin in a co-

Table 3 Randomized Trials of Primary Thromboprophylaxis in Pancreas Cancer

Reference	N	Drug	Chemotherapy	Median Survival	Notes
Maraveyas et al., ⁷⁷ 2009	123	Dalteparin	Gemcitabine	Lethal thrombosis and sudden death, 0% in dalteparin arm vs. 9% in control ($P = .028$); but "early death burden," 7% vs. 11% ($P = .62$). No overall survival difference	Reduction in primary end point of thrombosis (25% to 3.5% over first 100 d; 31% to 12% overall)
Riess et al., ⁷⁹ 2010	312	Enoxaparin	Gemcitabine-based (+/- 5FU/ cisplatin depending on performance status)	8 mo without enoxaparin, 8.3 mo with enoxaparin ($P = .501$); median follow-up time of 45 mo	Closed early because of significant symptomatic thromboembolism reduction 9.9% vs. 1.3% at 3 mo (primary end point); at 12 mo: 15.1% vs. 5.0%
NCT00031837 ^a	400	Dalteparin	Systemic gemcitabine	Pending (secondary end point)	Pending results, primary end point is quality of life
NCT00662688 ^a	136	Dalteparin	Gemcitabine +/- capecitabine	Pending (secondary end point)	Pending results, primary end point is thromboembolic event rate
NCT00966277 ^a	87	Dalteparin	Investigator choice	Pending (secondary end point)	Pending results, primary end point is thromboembolic event rate

^aClinicalTrials.gov identifier.

hort of patients with different malignancies, albeit in a more limited number of histologies. In this open-label, uncontrolled randomized protocol assessing safety and survival, 244 patients received nadroparin (weight-adjusted therapeutic doses for 2 weeks followed by half-therapeutic doses for an additional 4 weeks) versus no nadroparin ($n = 259$). Patients had either hormone-refractory prostate cancer, non-small cell lung cancer, or locally advanced pancreas cancer. No difference was observed in bleeding, time to progression, or overall survival. The median survival was 13.1 months in the nadroparin arm versus 11.9 months in the no-nadroparin arm (HR, 0.94; 95% CI, 0.75–1.18, adjusted for cancer type).

Prospective, Randomized Studies (Pancreas Cancer-Specific)

In 2009, an abstract by Maraveyas et al.⁷⁷ presented results of their phase IIb FRAGEM (Fragmin and Gemcitabine) trial, wherein patients with advanced pancreas cancer were randomized to gemcitabine or

gemcitabine with therapeutic-dose, primary prophylaxis dalteparin given for 12 weeks (200 IU/kg daily for 4 weeks, then 150 IU/kg daily for 8 weeks). The primary end point was reduction of thromboembolic events. The secondary end point was reduction of "early death burden," which they defined as death within 3 months of randomization, citing up to 25% of patients with advanced pancreas cancer in phase III trials dying within this time. The investigators hypothesized that prophylactic anticoagulation would impact this early mortality. Results from 64 patients in the control arm (61% with metastatic disease) and 59 patients in the gemcitabine plus dalteparin arm (44% with metastatic disease) showed thrombosis rates of 25% and 3.5% over the first 100 days, and 31% and 12% overall, respectively.⁷⁷ The rate of lethal thrombosis and sudden death was 0% in the dalteparin arm versus 9% in the control arm ($P = .028$), but the early death burden was 7% versus 11%, respectively ($P = .62$). No difference was seen in overall survival. The investigators therefore

concluded that the primary end point of thrombosis reduction was met, and a reduction in lethal thrombosis occurred with dalteparin. Despite the relatively small trial size, final results of the trial are anticipated.

Recently, the results from CONKO-004 were reported in abstract form.⁷⁹ In this multicenter prospective randomized phase III trial of chemotherapy with or without primary prophylaxis enoxaparin (1 mg/kg daily for 3 months, followed by 40 mg daily), the investigators accrued 312 patients with advanced pancreas cancer. The primary end point was reduction in symptomatic thrombosis, and secondary end points included toxicity, time to progression, and overall survival. The intention-to-treat analysis showed a significant decrease in symptomatic thrombosis after 3 months (9.9% in the chemotherapy alone arm vs. 1.3% in the enoxaparin arm) and 12 months (15.1% in the chemotherapy alone arm vs. 5.0% in the enoxaparin arm). No significant differences were seen in major bleeding events between the arms. Over a median follow up of 45 months, neither time to progression (5.4 vs. 5.0 months; $P = .941$) nor overall survival (8.0 vs. 8.3 months; $P = .501$) were significantly different between the chemotherapy alone and enoxaparin groups, respectively. However, this trial closed early after a data and safety monitoring committee decision confirming the early significant thrombosis reduction, and is therefore underpowered to observe a survival benefit between the arms.

Unreported Trials

A randomized controlled multicenter study (ClinicalTrials.gov identifier: NCT00031837) has completed accrual of 400 patients with advanced pancreas cancer receiving gemcitabine and is investigating the primary end point of quality of life, wherein patients receive primary prophylaxis dalteparin or placebo in addition to chemotherapy. Secondary end points include overall survival, frequency of symptomatic thrombosis, treatment complications, and safety. Trial NCT00662688 is a 4-arm randomized trial examining the effect of primary prophylaxis dalteparin on the thrombosis rate in patients with metastatic pancreas cancer receiving chemotherapy (gemcitabine with or without capecitabine). Trial NCT00966277 is a randomized protocol with details similar to those of NCT00662688, although with investigator choice of chemotherapy. NCT00426127 was a nonrandomized phase II trial of docetaxel,

liposomal doxorubicin, and primary prophylaxis enoxaparin in patients with advanced pancreas cancer; however, it closed early because of poor accrual for a planned 27 patients.

Conclusions

Pancreas cancer remains an extraordinarily difficult malignancy to treat, and represents one of the most common, if not the commonest, malignancy associated with thrombosis (Table 4). An understanding of the pathogenic underpinnings of pancreas-related thrombosis has evolved over the past several years, providing opportunities for therapeutic interventions. Thromboses and particularly early thromboses have poor prognostic import. Research has clearly shown the importance of anticoagulation, particularly with low-molecular-weight heparin, after the diagnosis of a thrombosis in a patient with malignancy. As of now, however, prophylactic anticoagulation for patients without known thrombosis is not routinely recommended for patients with advanced pancreas cancer outside of a clinical trial. Data maturation from recently completed trials may add insight, but future trials should examine survival as a primary end point and focus on specific patient

Table 4 Key Points in Pancreas Cancer Thrombosis and Anticoagulation^a

- Numerous clinical and molecular factors contribute to thrombogenicity in pancreas cancer.
- The relatively high incidence of thrombosis and its contribution to morbidity and mortality in pancreas cancer calls for vigilance in diagnosis and treatment of these events.
- Superficial vein thrombosis with proximity to the deep venous system should be treated with at least 4 weeks of anticoagulation (category 2B⁸⁷) unless the thrombosis is catheter-associated and the catheter is removed.
- Deep vein thrombosis, including pulmonary embolism, should be anticoagulated.^b
- Primary prophylactic anticoagulation of hospitalized patients with pancreas cancer is recommended.
- Primary prophylactic anticoagulation of outpatients with pancreas cancer should be performed only in the context of a clinical trial.

^aRisk of bleeding must always be considered in the decision to initiate anticoagulation.

^bDuration of anticoagulation treatment for deep vein thrombosis is indefinite for as long as pancreas cancer is active, and low-molecular-weight heparin is recommended over warfarin.

populations. Additionally, pending investigation in the oncology population, the newer-generation oral anticoagulants may ultimately prove to be an additional option (with greater convenience to patients but likely higher cost) for the secondary and perhaps even primary prophylaxis of thrombosis in select patients. Tailoring therapy or focusing investigations to specific patient subsets, such as those presenting with thrombosis concomitant with their pancreas cancer diagnosis, or with high levels of procoagulant molecules, such as tissue factor, may be a justified area of future study. Speculatively, it is possible that treatment stratification based on thrombosis timing/burden in pancreas adenocarcinoma may be entertained going forward.

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CME Activity: Thromboembolism in Pancreatic Cancer

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Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate.

- You are seeing a 66-year-old man with a recent diagnosis of pancreatic cancer. You know that this diagnosis places him at high risk for thromboembolic events. Which of the following factors is most significant in promoting a higher risk of thromboembolism among patients with pancreatic cancer?
 - Non-A blood type
 - A low or normal platelet count
 - Normal levels of D-dimer
 - The use of erythropoietin-stimulating agents
- You consider initiating primary prophylaxis against thromboembolism for this patient. What is the general recommendation regarding this practice in the setting of pancreatic cancer?
 - It is not part of routine care
 - It should be initiated only among patients over the age of 65 years
 - It should be initiated only among women
 - It is now considered to be the standard of care
- The patient develops a lower extremity deep venous thrombosis. Which of the following agents is most preferred for management of thrombosis?
 - Warfarin
 - Dabigatran
 - Low-molecular-weight heparin
 - Unfractionated heparin
- You initiate therapy with the recommended treatment. Based on available prospective studies, which of the following outcomes is most likely with antithrombotic therapy?
 - A higher risk of bleeding
 - A lower risk of thromboembolic events
 - A reduction in cancer progression
 - A higher rate of overall survival

Activity Evaluation

1. The activity supported the learning objectives.	3. The content learned from this activity will impact my practice.
Strongly Disagree	Strongly Disagree
1 2 3 4 5	1 2 3 4 5
2. The material was organized clearly for learning to occur.	4. The activity was presented objectively and free of commercial bias.
Strongly Disagree	Strongly Disagree
1 2 3 4 5	1 2 3 4 5

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