Thromboembolism Is Common and Influences Prognosis in Patients With Pancreatic Cancer, Study Reports

A recent study confirms that thromboembolism (TE) is a significant risk in patients with exocrine pancreatic cancer, showing a 36% incidence as well as conferring a worse prognosis (Cancer [published online ahead of print October 11, 2011] doi: 10.1002/cncr.26600).

Study Methods and Findings
Andrew Epstein, MD, professor in the division of gastrointestinal medical oncology at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City, and colleagues conducted a review of patients with pancreatic cancer to assess the impact and timing of TE on survival and to examine associations between other clinical variables and risk of TE.

Using an institutional electronic application, investigators identified patients with pancreatic cancer who were treated with chemotherapy at MSKCC from January 1, 2000 through December 31, 2009. Any patient records found by the electronic application to have a diagnosis code indicating TE were then manually reviewed for data. In addition, to verify the accuracy of the electronic application in selecting records relevant to this study, 50 randomly selected charts from patients with pancreatic cancer but no coded TE event were reviewed manually and none were found to have had a TE. Eight patients who were diagnosed with a TE more than 3 months before the diagnosis of pancreatic cancer were excluded from analyses.

The median survival of the 1915-patient cohort was 13.7 months, and 690 patients (36%) had at least one TE recorded. Of the 690 patients with TE, 614 (89%) had a non–catheter-related deep vein thrombosis and/or pulmonary embolism. An arterial TE occurred in 30 patients (4.4%). A total of 638 patients (92.5%) had locally advanced or metastatic disease when their first TE was diagnosed.

After adjusting for pancreatic surgery, having a TE significantly increased the risk of death during the follow-up interval with a hazard ratio (HR) of 2.6 (P < .01). Not surprisingly, patients who underwent surgery had significantly longer survival than those who did not undergo surgery (HR, 0.42; P < .01). The 134 patients who developed a TE within 1.5 months from the diagnosis of pancreatic cancer had a significantly higher risk of death than patients who did not develop a TE within 1.5 months of their cancer diagnosis (HR, 2.1; P < .01).

“It is not a new observation to find that TE is common in pancreatic cancer, but this study helps to define the incidence. The main new finding is that patients with an early TE had clearly worse outcomes,” says corresponding author Eileen O’Reilly, MD, associate member of the gastrointestinal oncology service at MSKCC and an associate professor at the Weill Cornell Medical College of Cornell University.

Time to the diagnosis of TE was significantly shorter in patients who received erythropoiesis-stimulating agents (ESAs) versus those who did not. Having a low body mass index (BMI) (< 18.5 kg/m²) compared with a normal BMI was associated with a significantly longer time to thrombosis (HR, 0.6; P < .01), but having an overweight or obese BMI (≥ 25 kg/m²) compared with a normal BMI was not associated with time to thrombosis.

Investigators found no significant effect of a lower hemoglobin level, higher white blood cell count, higher platelet count, or elevated activated partial thromboplastin time values. Time to thrombosis, however, was significantly shorter for patients with elevated international normalized ratio (INR) values (HR, 1.22; P < .01).

In a multivariate Cox regression analysis of overall survival controlling for standard clinical variables such as age and sex as well as variables that were found in the study to be significantly associated with time to thrombosis on bivariate analysis, having a TE was associated with an increased risk of death (HR, 2.83). Gender or ESA administration...
had no effect, but an older age at diagnosis and an elevated INR were associated with significantly worse survival.

“This data reinforces the inverse association of thromboembolism and pancreatic cancer outcomes: an important, well-recognized, but not well-dealt with issue,” says Wasif M Saif, MD, MBBS, medical director of the Pancreas Center at Columbia University College of Physicians and Surgeons in New York City.

Clinical Implications

According to the authors, this is the first pancreatic cancer-specific study to show that early TEAs are associated with shorter survival. They suggest that one implication of the trial is that early TE be considered as a stratification factor for future clinical trials because of the poorer prognosis associated with it.

This analysis of the association between clinical variables and the timing of thrombosis is also unique. ESA administration and an elevated INR were associated with the earlier diagnosis of TE, with a low BMI lengthening the time to thrombosis. Furthermore, an elevated INR was associated with worse overall survival.

The authors admit several limitations of their study, including:

- Cause of death was not obtained in all 690 patients with TE.
- The search tool used was subject to human error.
- Chemotherapy treatment was not included in the analysis.
- Performance status was not obtained.
- The effects of recurrent TE were not considered.
- Stage data in patients without thrombosis were not examined.
- Fluid retention states that may affect BMI were not considered.

“It would be worth stratifying the study patients with thromboembolism according to stage, treatment strategies, and time elapsed between the development of thromboembolism and death,” Dr. Saif says.

Still, the study shows that TE, especially early TE, predicts for worse survival. Dr. O’Reilly says the question then becomes, “Is there anything biologically we can do to alter this?” Two reported trials of thromboprophylaxis in patients with advanced pancreatic cancer show a decrease in the incidence of TE, but were not powered to detect an overall survival benefit (Eur J Cancer. 2009;7(suppl):362; and J Clin Oncol. 2010;28(suppl 15):4033).

Perhaps early thromboprophylaxis might improve survival and ongoing trials may help answer this question (NCI clinical trial identifiers NCT00966277, NCT00662688, and NCT00031837). “We have data showing that the low molecular weight heparins can be used safely and effectively in advanced pancreatic cancer patients, but prospective data showing survival improvement is lacking,” Dr. Waif says.

Until prospective trials show a benefit, routine thromboprophylaxis for patients with pancreatic cancer should not be administered. “Unfortunately, the ongoing trials do not have overall survival as an endpoint, so the question of benefit of thromboprophylaxis will not be fully answered,” Dr. O’Reilly says. “As the more convenient oral anticoagulants become available, I think this question will be revisited because of increased ease of treatment for a pancreatic cancer patient facing multiple other issues.”