

## HIGHLIGHT ARTICLE

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# Pancreatic Cancer and Thromboembolism in the Ambulatory Community

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### Summary

Pancreatic exocrine adenocarcinoma is one of the most common malignancies associated with thromboembolism. The authors summarize the two abstracts (#368 and #273) presented at the 2012 ASCO Gastrointestinal Cancers Symposium which were focused on pancreatic thrombosis in ambulatory patients. In addition, they discuss the risk of thrombosis associated with malignancy, chemotherapy, and erythropoietin stimulating agents and the management and implications thereof.

### What We Knew Before the 2012 ASCO GI Cancers Symposium?

Pancreatic cancer and chemotherapy are both well-known risk factors for thromboembolism. Advanced pancreatic cancer has been shown to increase the risk of thromboembolism to as high as 1 in 5 cancer patients, while chemotherapy further increases that risk 5 times [1, 2]. However, the difference in risk associated with ambulatory patients vs. bed bound patients has not been well characterized, as there are few studies analyzing this population's risk. One British study that looked at ambulatory patients seen at an outpatient deep vein thrombosis clinic noted an overall cancer-associated rate of venous thromboembolism (VTE) to be 13.6% [3]. Another prospective study that focused on ambulatory patients receiving chemotherapy showed that 9.2% of deaths in this population were due to thromboembolism [4]. At present, the American Society of Clinical Oncology (ASCO) guidelines on venous thromboembolism prophylaxis include low-molecular-weight heparin (LMWH) administration to all hospitalized cancer patients (if no contraindication), but the guidelines do not recommend “routine prophylaxis of ambulatory cancer patients with anticoagulation ... with the exception of patients receiving thalidomide or lenalidomide” [5]. Thus, at present, outpatient deep

vein thrombosis prophylaxis is uncommon and not clinically recommended.

Erythropoietin is another medication that is widely used in cancer patients, but has not been adequately evaluated. The drug is most commonly used in doses of 50 units/kg three times a week to treat anemia in patients with chronic renal failure. However, in cancer patients with chemotherapy-induced anemia, it can be used in doses up to 500 units/kg weekly. Venous thromboembolism have been specifically noted in cases where the hemoglobin goes above 120 g/dL, the hemoglobin level increases to values greater than 12 g/dL or the hemoglobin increases at a rate of more than 1 g/dL every two weeks [6]. While all doses of erythropoietin stimulating agents result in a higher incidence of thrombotic events, the higher dose used in cancer patients only increases that risk, and few studies have weighed the risks and benefits of the drug.

### What We Learnt at the 2012 ASCO GI Cancers Symposium?

#### Chemotherapy and Risk of Venous Thromboembolism in Patients with Pancreatic Cancer (Abstract #368 [7])

Blanco *et al.* performed a retrospective study in which they analyzed the incidence of thrombosis in ambulatory pancreatic cancer patients who were receiving chemotherapy (predominately gemcitabine-based regimens as well as fluoropyrimidines-based regimens and platinum-based regimens). Among the 64 patients included in the study, 20 experienced venous thromboemboli:

- 7 pulmonary emboli;
- 8 deep vein thromboses;
- 8 visceral vein thromboses; and
- 2 experienced arterial thromboemboli.

**Key words** Ambulatory Care; Carcinoma, Pancreatic Ductal; Hematinics; Venous Thromboembolism

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**Table 1.** Summary of results by Lin *et al.* (Abstract #273 [8]).

	Cancer patients	Control patients
Mean Charlson comorbidity index	6.8	6.0
Venous thromboembolism incidence	19.2%	1.4%
Bleeding	23.4%	7.0%

Using Horana's predictive model for chemotherapy-associated thrombosis, the rates of venous thromboembolism in the high-risk group and intermediate risk groups respectively were 31.8% and 35.3%. This study supports the fact that pancreatic cancer patients on chemotherapy have a high risk of venous thromboembolism, and suggests that using a predictive model we can identify at risk patients.

#### Chemotherapy and Erythropoietin Stimulating Factors and Venous Thromboembolism in Pancreatic Cancer (Abstract #273 [8])

Lin *et al.* also studied venous thromboembolism in ambulatory patients by doing a retrospective analysis comparing patients with pancreatic or other solid tumors and a matched control cohort of patients without cancer, looking at the incidence of deep vein thrombosis, pulmonary embolism, and deep vein thrombosis plus pulmonary embolism during a follow-up period of 3-12 months after chemotherapy initiation. Venous thromboembolism occurred in 19.2% of the cancer cohort compared with 1.4% of the control cohort, highlighting the increased risk associated with both malignancy and chemotherapy (Table 1).

The study also looked at the use of erythropoietin stimulating agents, noting these medications to have a correlation with venous thromboembolism (OR 1.71).

The study therefore demonstrates that even ambulatory patients have a profound risk of venous thromboembolism when they have cancer and are undergoing chemotherapy, and that erythropoietin stimulating agents should be used cautiously as they increase that risk.

#### Discussion

These studies by Blanco and Lin both demonstrate that pancreatic malignancy and chemotherapy substantially increase morbidity and mortality in the ambulatory community. Lin's study also evaluates the association between erythropoietin stimulating agents and venous thromboembolism, highlighting the importance of using clinical judgment with this potentially deadly class of drugs.

Thromboembolic events such as pulmonary embolism, arterial or deep venous thrombosis and cerebral ischemic stroke are rare but known complications during chemotherapy for solid tumors [9]. Erythropoietin stimulating agents are approved for the treatment of anemia in patients with nonmyeloid malignancies whose anemia is due to the effect of concomitantly administered chemotherapy. The risk of

thrombovascular events associated with erythropoietin stimulating agents was lately assessed by the Oncologic Drugs Advisory Committees in 2004 and 2007 [10]. Six studies (Breast Cancer Erythropoietin Survival Trial; Evaluation of NeoRecormon on outcome in Head And Neck Cancer in Europe; Danish Head and Neck Cancer; Lymphoid Malignancy; CAN-20; and Anemia of Cancer) investigating erythropoietin stimulating agents in oncology patients showed increased risk of thromboembolism when administered to achieve hemoglobin levels equal to, or greater than, 12 g/dL in patients with non-myeloid malignancies.

The studies presented at the meeting focus on only pancreatic cancer patients and offer evidence that perhaps deep vein thrombosis prophylaxis should be considered in this population in the future. In addition, these studies highlight how imperative it is that physicians be aware of this risk, and potentially prophylaxis accordingly. Additional studies are needed to better characterize these risks.

**Conflicts of interest** The authors have no conflicts to disclose

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