Venous Thromboembolic Disease and Occult Malignancy

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Venous thromboembolism (VTE) is a major cause of morbidity and mortality in the medical and surgical patient. Deep vein thrombosis (DVT) and pulmonary embolism (PE) as well as venous catheter thrombosis are more prevalent in the cancer patient than in the general population. While there is an increase risk of VTE in the cancer patient, the reverse is also true: Those with newly diagnosed VTE have a higher risk of harboring occult malignancy. The association between newly diagnosed VTE and occult malignancy has led investigators to attempt to identify a screening strategy for occult malignancy in the setting of newly diagnosed VTE.

Cancer is a known risk factor for the development of venous thromboembolism. Population based studies have noted malignancy to increase the likelihood of VTE by 4-6 times with metastatic disease increasing the odds ratio of VTE to as high as 20.[5,11] There are multiple mechanisms behind this increased risk including direct biologic effects of tumor, indwelling catheters, chemotherapy causing endothelial damage and direct compression and/or invasion of vessels by tumor. The risk of VTE recurrence as well as major bleeding during anticoagulation is higher in those with malignancy with hazard ratios as high as 3.2 and 4.1 respectively. [14,19,26] Because of this fact, there have been multiple trials looking at the benefit of different types of anticoagulation for VTE in cancer patients. Trials with low molecular weight heparins such as dalteparin have shown significantly less episodes of recurrent VTE without additional bleeding episodes. [18] Because the risk of recurrence is high in ongoing malignancy, most sources recommend continued anticoagulation with either coumadin or preferably LMWH until the malignancy is cured. [16]

The biologic interaction between tumor cells, macrophages, platelets and the coagulation system has become an area of great interest. The complex interaction between individual cancer cell types and the coagulation system may explain why there appears to be heterogeneity in the risk of developing VTE across cancer types. Levitan and colleagues looked at 8 million medicare records and found that while the absolute

risk of VTE was highest in those cancers that were most prevalent (lung, prostate and colon), the relative risk of developing VTE was highest in Ovarian, Brain, Pancreatic and Lymphoma.[19] It appears as if individual tumor cells may modulate the coagulation system to a different extent. It is coming to light that there may be a two-way relationship between the activation of the coagulation system by cancer and the continued growth of tumor cells, specifically with respect to angiogenesis. [11] It has been noted that tissue factor, constitutively expressed on most cancer cells, plays a large role in the upregulation of angiogenic factors including VEGF. VEGF in turn upregulates tissue factor in a positive feedback loop. [4] The theoretical potential for anticoagulation with heparins to not only treat VTE but perhaps offer antineoplastic effects was strengthened by a meta-analysis of clinical trials comparing LMWH and UFH for initial treatment of acute VTE. [9,13] The meta-analyses, although inherently limited by its design, revealed a 3-month mortality benefit from LMWH not explained by a reduction in fatal PE or bleeding suggesting a possible antineoplastic effect. Several prospective randomized trials have subsequently reported survival benefit with LMWH vs placebo as an adjuvant to chemotherapy [2,15] and confirmatory studies are in process.

While it is clear that cancer leads to increased risk of VTE, the reverse is also true. Newly diagnosed VTE, especially in the absence of known risk factors (i.e. primary or "idiopathic" VTE), portends an increased risk of occult malignancy. Armand Trousseau first described this link between thromboembolic disease and occult malignancy in a series of lectures printed in 1867. [28] The association between thrombophlebitis and occult malignancy was later termed "Trousseau's Syndrome". Subsequently, studies began to surface which supported this association including a cohort study in 1951 by Ackerman documenting a 9% incidence of occult malignancy in patients with thromboembolic disease[1]. Multiple population based studies and cohort studies have also supported this initial finding[7,8]. Hettiarachchi et al noted that the association appears to be strongest in those who have idiopathic VTE (iVTE)[12]. In this study, 326 patients with known DVT were separated into those with DVT secondary to known risk factors (e.g. recent surgery, pregnancy, prolonged immobilization) and those with unexplained or "idiopathic" DVT. Those with iVTE had a significantly higher

occurrence of malignancy with a relative risk of 4.6. Another study by Murchison in 2004 looked at approximately 60,000 patients with iVTE followed over 19 years and found a standardized incidence ratio (SIR) of 2.9 for the diagnosis of cancer in the 12 months following iVTE. [22] Multiple studies have confirmed this association with SIRs as high as 5.27. [3,20,22,23,27] Notably, cancer risk seems to decrease over time and the cancer incidence approaches that of the normal population after approximately 2 years post VTE. It appears that the association between iVTE and malignancy is greatest in the first 6-12 months. Furthermore, it has been shown that in instances of recurrent iVTE, the risk of developing malignancy is as high as 17%. [25]

Given the risk of occult malignancy in iVTE, several authors have attempted to delineate a reasonable screening method in hopes of diagnosing malignancy at the earliest possible stage. Generally, there are two basic camps: basic routine screening versus an aggressive initial screen including tumor markers, advanced imaging and invasive procedures. Several cohort studies have looked at iVTE and the value of different levels of screening for malignancy and recommend only routine targeted screening. In 1996, Cornuz and colleagues published a retrospective cohort study looking at 142 patients with iVTE and following them over 34 months. 16 of the patients were diagnosed with malignancy during the hospitalization for their iVTE. In retrospective analysis of the clinical evaluation, all 16 patients had an abnormality on either routine history and physical, basic labs including CBC, LFTs and hemeoccult or chest x-ray. Only 3 patients developed cancer in 34 mo follow up, one of whom had anemia on presentation, giving this basic routine screening method a sensitivity of 89%. This led the authors to conclude that a comprehensive history and physical, routine laboratory testing and chest radiography would be appropriate for detecting cancer and that additional testing should be based only on abnormalities identified from the initial routine assessment. [6] Another study by Nordstrom looked at a cohort of 3795 patients with suspected DVT from the Swedish tumor registry. 66 patients in the DVT group were diagnosed with cancer within 6 months, significantly more than those without DVT. Of those, 38/66 or 57.6% were diagnosed using routine screening, Further analysis of the 28 patients with occult cancer not initially detected revealed only 11 patients who did not have metastases.

Of these only 2 would have benefited from early diagnosis based on review of age, general health and tumor type. [23] Nordstrom and colleagues thus agreed with Cornuz and concluded that initial aggressive screening with advanced imaging or procedures would not be cost effective.

Several other cohort studies have come to a different conclusion. In 1991, Monreal prospectively followed 113 patients with VTE after a more extensive preliminary cancer screen which added carcinoembryonic antigen (CEA), erythrocyte sedimentation rate (ESR), upper endoscopy (EGD), and abdominal ultrasound or abdominal CT scan to the routine workup. They found 11 cancers on initial evaluation of which 6 had no findings on history and physical, however 2 had CBC abnormalities and 1 had perihilar mass on CXR. One cancer (a basal cell skin CA) was missed by the initial screen. Several of the cancers revealed by the more aggressive screening modalities (abdominal US and CT) were noted to be very early stage. The conclusion was that routine screening for initial VTE should include CEA, ESR, LDH and US of the abdomen or CT of the abdomen. [20] Interestingly, no urinalysis was obtained which may have picked up the 2 stage I transitional cell bladder carcinomas seen on abdominal imaging. Building on this idea, in 2004 Monreal looked at 864 patients with VTE and no known malignancy or prior VTE and prospectively followed them for a period of 12 months. All patients were initially screened with complete history and physical, routine labs (this time including ESR, SPEP and urinalysis) and chest x-ray. For those who did not have malignancy following the initial screen, an additional limited work up including CEA, PSA (for men) and CA-125 (for women) as well as abdominal ultrasound was obtained. They noted that only approximately half of patients with malignancy were identified with routine screening. Of the remainder, 61.5% of the cancers picked up with the limited cancer screen vs. only 14.3% of those discovered by routine follow up had early stage disease. The authors not only concluded that the limited screen in addition to routine screening was beneficial, but that further more aggressive screening may be indicated to maximize the number of patients identified with early disease and curative potential. [21]

There are many problems with trying to interpret the results of these cohort studies. The most important is that, despite studies showing more cancers found at an earlier stage, there is no way to tell if this translates into decreased cancer-related mortality. In an effort to address this, Piccoli published a randomized multi-center clinical trial in 2004.[24] In this well-designed study, 1,020 patients with VTE were carefully screened for secondary causes of VTE including malignancy diagnosed by routine screening at time of accrual. They were able to randomize 201 patients with iVTE and no evidence of malignancy by routine screening consisting of history and physical, cbc, chem 7, calcium, urinalysis, liver function tests and chest x-ray. 99 patients were randomized to an extensive malignancy screening and 102 patients were randomized to the control group. The control group were followed at 3 months, 12 months and 24 months with history and physical and *were not told about their enrollment in the study*, using the Zelen design for randomization. [29] Those randomized to the extensive screen were offered ultrasound of the abdomen and pelvis, CT scan of the abdomen and pelvis, EGD, colonoscopy or sigmoidoscopy with double barium swallow, hemeoccult, sputum cytology and tumor markers including CEA, alpha fetal protein (AFP), PSA for men and CA-125 for women. 80% of the patients in the aggressive screening group obtained all of these screening tests. In addition, women received PAP smear and mammography and men were offered abdominal prostate ultrasonography. All of these studies had to be completed within 4 weeks of enrollment. The primary outcome was cancer related mortality as defined as death due to cancer or complications of diagnostic or therapeutic procedures used to diagnose or treat the cancer.

The results of this study were interesting. Foremost, the primary outcome was not met. While there was a trend toward decreased mortality in the thorough screening group (2% vs. 3.9%), this did not reach statistical significance. Nonetheless, on further analysis the study did provide some important results. First, despite 80% of the intervention group receiving the full battery of invasive testing, there were no serious complications. Additionally, aggressive screening detected malignancy with a sensitivity of 93%. Cancers identified by the screening group were also found an average of 10.6 months earlier and were less advanced than the control group with 9/14 vs. 2/10 patients with

stage 1 or 2 disease respectively (P<0.047). Notably, the study accrued only approximately 20% of the expected 1000 patients necessary to adequately power the study. The author comments on this saying that only 5 of the over 40 trial centers were able to enroll patients secondary to ethics committee rejection of the Zelen randomization procedure. That is, they felt it was unethical to enroll a patient in a study as a control without telling them they would be in a trial. Conversely, many investigators were uncomfortable informing a patient about a study where there is a 10% chance that they may have cancer and that if they enroll in the study there is a 50% chance that their doctor will do no further screening! The ethics of the Zelen procedure for randomization is discussed further in a nice article by Hawkins. [10]

At this time, the depth and aggressiveness of screening for occult malignancy in those with iVTE is unclear and no consensus statement has been drafted. On one hand, the data regarding the risks of occult cancer in those with iVTE are compelling, leading one to attempt to uncover a malignancy as soon as possible. The idea that cancer can be identified at an early and potentially curable stage is always the goal. One could argue that malignancy is usually only curable in the earlier stages, making this sort of screening reasonable. However, aggressive screening does come at a cost. While Piccioli's study suggests that aggressive screening may be safe with respect to patient morbidity, there have been no studies to date looking at the financial cost of an aggressive initial screening protocol. Nonetheless, there was a trend toward decreased mortality and earlier stage at diagnosis in the only randomized controlled trial to date looking at this issue. Despite this trend, the argument by Lee in his 2006 review in Hematology is that there remains no convincing evidence that aggressive screening reduces mortality and furthermore, there has been no evaluation of the likely major financial and emotional costs. [17]

A reasonable approach after evaluating the evidence may be the following:
For all patients with newly diagnosed VTE, initiate a thorough history and physical exam catered toward the evaluation of occult malignancy. This should include breast exam, pelvic exam, rectal exam and thorough lymph node evaluation. Routine lab work should

include CBC, chemistries including calcium, LFTs, urinalysis and hemeoccult. A good quality PA and lateral chest x-ray should be obtained. The patient should also undergo a thorough screen for congenital and acquired thombophilias. If the patient is within the screening range for the common malignancies and has not been screened, this should be done in a timely fashion including mammography, colonoscopy, PAP smear and arguably PSA screening. If the patient is found to have idiopathic VTE, further screening with EGD and CT of the Chest, Abdomen and Pelvis may be considered. If the patient has recurrent iVTE, the aggressive initial screen proposed by Piccoli should be considered.

In the end, I cannot help but relate to the designers of the Piccioli trial. I will have a hard time telling my patient with newly diagnosed iVTE that there is a 10% chance that he or she will develop a malignancy within the next 2 years, but that the only randomized trial for aggressive screening only showed a *trend* toward improved survival so we are going to hold off on that CT scan. As pretest probability for occult malignancy increases from secondary VTE, to primary VTE to recurrent primary VTE, a similar increase in the aggressiveness of cancer screening should follow.

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