Cancer and Blood Clots: Clinical Corner

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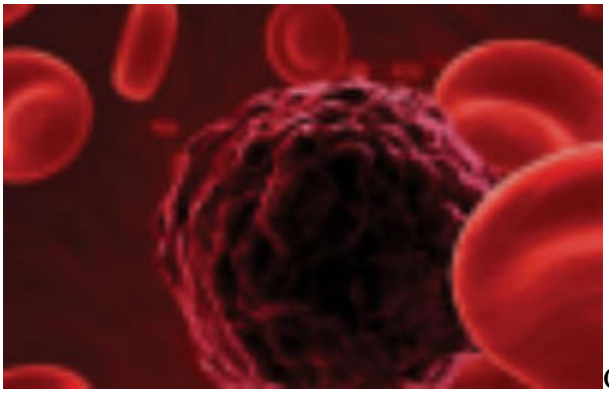
According to the National Cancer Institute, there are approximately 11 million living America ns who have been affected with cancer, and about 1.4 million who were newly diagnosed in 2008.



Cancer is a risk factor for developing blood clots (or thrombosis), both in the arteries and veins. Venous thrombosis can occur in the deep veins of the extremities, referred to as deep vein thrombosis (DVT), or in the lungs, referred to as pulmonary embolism (PE). Taken together, DVT /PE are commonly referred to as venous thromboembolism or VTE . Approximately 20% of all VTE s occur in patients with cancer1. The risk for VTE in cancer is determined by a number of co-existing factors which may be broadly divided into general risk factors [age, race, obesity, past history of VTE , coexisting medical conditions, inherited and acquired thrombophilias] and cancer specific risk factors [cancer site, stage, type of chemotherapy, hormonal therapy, surgery]. The goal of this article is to review the

risk of VTE in cancer patients in different clinical settings, and to discuss strategies for prevention and treatment of VTE in cancer patients. These issues are discussed under commonly encountered clinical scenarios and I expect that most patients with cancer will fall under one or more of these scenarios.

The Venous Thromboembolism (VTE) patient without history of cancer

Should patients with newly diagnosed, unprovoked VTE be concerned about underlying cancer?

Unprovoked VTE refers to the situation where VTE occurs in the absence of known risk factors, such as prolonged immobilization, surgery, trauma, and estrogen use. Thrombosis can be the first sign of cancer. It is estimated that about 10-15% of patients with unprovoked VTE will be diagnosed with a cancer over the next 1-2 years. Does this mean all patients with a newly diagnosed, unprovoked VTE should undergo cancer screening? This question was the basis of a recent meta-analysis where data from 34 studies in the literature were evaluated to assess: 1) if screening for cancer in patients with unprovoked VTE was beneficial; and 2) whether there was a difference between limited screening (detailed history, physical examination, laboratory testing and chest x-ray) and extensive screening (ultrasonography or CT imaging of the abdomen and pelvis, measurement of tumor markers like prostate specific antigen, carcinoembryonic antigen and cancer antigen-125).

This study found that 6% of patients with unprovoked VTE had a previously undiagnosed cancer at the time of the VTE. This increased to 10% at 12 months after VTE diagnosis. In addition, the extensive screening approach identified more undiagnosed cancers than limited Clinical Corner: Cancer and blood clots Raj Kasthuri, MD University of North Carolina at Chapel Hill screening. However, this study was unable to answer two important questions: 1) whether a significant number of cancers detected with this screening approach were early-stage cancers, and therefore, more amenable to cure; and 2) if detecting the cancers earlier resulted in decreased cancer associated morbidity and improved overall survival in these patients2. It is important to realize that such extensive screening is associated with adverse consequences, such as exposure to invasive diagnostic procedures, patient anxiety, potential for false positive test results, and increased cost. Therefore, the answer to the question of whether patients with unprovoked VTE should undergo screening for underlying cancer is, at the present time – NO. While cancer should be considered in selected patients, such as the elderly, those with recent weight loss, etc., routine screening in all patients with unprovoked VTE is not recommended.

The cancer patient without history of VTE

What does a person with newly diagnosed cancer who has never had a blood clot need to know about risk for VTE?

Cancer is an independent risk factor for VTE. Patients with cancer are approximately four times more likely to develop VTE compared to the general population3,4. However, it is important to recognize that this risk varies depending on the type of cancer and certain cancers are associated with higher risk for VTE than others. Cancers associated with the highest risk for VTE include brain cancer, pancreatic cancer, stomach cancer, ovarian cancer and hematological (blood)

cancers like lymphoma and myeloma [specifically myeloma treated with certain types of chemotherapy]5,6. Examples of cancers that are associated with relatively low risk for VTE include breast and skin cancers.

Another important consideration is the treatment for cancer. Chemotherapy can result in activation of the clotting system and confers additional risk for thrombosis. The risk for VTE in cancer patients receiving chemotherapy increases from 4 to about 6.5 fold higher than that in the general population3. Certain chemotherapy drugs, either alone or when used in combination, are more likely to provoke thrombotic events than others. Asparaginase, a drug used in the treatment of certain types of leukemias, is a well known risk factor for thrombosis7,8. Other chemotherapy drugs that have been associated with risk for VTE include Cisplatin, Adriamycin®, 5-fluorouracil, Bleomycin, and Mitomycin. In general, the use of combination chemotherapy regimen, as is done frequently in the treatment of cancer, appears to be associated with an increased risk of thrombosis9. The risk associated with hormonal therapy is discussed later.

In some instances, medications that do not confer an increased risk for VTE when used alone can do so when they are combined with other drugs. A good example of this is the combination of high dose steroids and thalidomide for the treatment of myeloma in which VTE rates as high as 20-30% per year have been reported10. These patients are therefore simultaneously started on thromboprophylaxis (preventive blood thinning therapy) with low molecular weight heparins (Lovenox®, Fragmin®, etc.) or warfarin (Coumadin®, Jantoven®), or the dose of steroids is decreased in order to decrease the risk for VTE.

A new class of anti-cancer drugs called anti-angiogenic agents bears special mention. This group of drugs is believed to act by preventing the development of new blood vessels in cancers. An example of an anti-angiogenic agent is Bevacizumab (Avastin®), which is frequently used in combination with other chemotherapy drugs for the treatment of colon cancer, among others. A recent analysis of studies using Bevacizumab found an increased risk for both arterial and venous thrombosis with the use of this drug11. The chemotherapy agents associated with the greatest risk of VTE are outlined in Figure 1. As new and novel approaches are developed for the treatment of cancer, it is important to consider the potential unintended adverse events such as the development of thrombosis.

In addition to the risk for VTE associated with the cancer and treatment with chemotherapy drugs, there are additional risk factors for VTE in cancer patients. First, a number of cancer patients undergo surgery – either for removal of tumors or as part of the diagnostic work-up. Surgery in itself is a well know risk factor for VTE although the risk varies depending on the location and extent of surgery. For example, abdominal surgery and neurosurgery appear to be associated with greater thrombotic risks as compared to other surgeries. Secondly, a number of cancer patients have central catheters placed for long term venous access for administration of chemotherapy. Catheter related thrombosis can occur in such patients. A recent study found that catheter related thrombosis occurs in about 5% of patients with long term venous catheters12. In addition to the adverse effects associated with DVTs in general, catheter related thrombosis in cancer patients can also lead to delay in administration of chemotherapy and transfusion of blood products. Finally, prolonged immobilization associated with surgery, frequent hospitalizations

for administration of chemotherapy, and dehydration are also encountered in patients with cancer, all of which are risk factors for VTE.

Thus, patients with cancer have multiple risk factors for VTE. Therefore all patients with cancer should discuss preventive measures with their doctors to prevent blood clots.

The cancer patient with recently diagnosed VTE

What does the cancer patient recently diagnosed with VTE need to be aware of ?

The development of VTE in patients with cancer has many implications pertaining to the treatment of cancer, risk for recurrence of VTE, and overall survival. As in any other setting, VTE in cancer is treated with anticoagulation (discussed later). A common side effect of chemotherapy is the development of low blood counts secondary to suppression of the bone marrow by these drugs. Although this decrease in blood counts is a transient phenomenon usually lasting no more than a few days, it still necessitates withholding of anticoagulation until blood counts recover given the associated increased risk for bleeding. Therefore, more often than not, anticoagulation is frequently interrupted in patients with cancer who are receiving chemotherapy. Despite this, the risk of bleeding complications is higher in cancer patients treated with anticoagulation (12.4% per year) compared to the general population13. The risk for VTE recurrence is also higher in cancer patients and about three-fold greater than in those without cancer (20.7% per year versus 6.8%)13. Both bleeding following anticoagulation and VTE recurrence appear to be associated with the severity of the cancer and tend to occur within the first 1- 2 months of VTE diagnosis. Finally, the occurrence of VTE in cancer is associated with a worse overall survival compared to cancer without VTE. A Danish study compared the survival of patients with VTE and cancer to age, sex, and cancer-type matched control patients without VTE and found that the overall survival in cancer patients with VTE was 2.2 fold shorter at 1 year compared to those without VTE14.

Overall, the diagnosis of VTE in patients with cancer is associated with a poorer prognosis. This further underscores the need for aggressive thromboprohylaxis in cancer patients to prevent the development of VTE.

Treatment of VTE in cancer patients

Does the treatment of VTE differ among cancer patients compared to the general population?

The answer is – YES. Most patients with VTE are generally treated with warfarin (Coumadin®). In such cases heparin is used in conjunction with warfarin for the first 5 to 7 days for “bridging” purposes and is discontinued once the PT/INR (the test used to monitor warfarin therapy) is within the target range (usually an INR in the 2-3 range). The form of heparin used can be unfractionated heparin (UFH) given intravenously (in the vein) as a continuous infusion; low molecular weight heparins (Lovenox®, Fragmin®, Innohep®) given as subcutaneous shots (under the skin) once or twice daily; or daily fondaparinax (Arixtra®) given subcutaneously.

Treatment of VTE in cancer patients is different in that low molecular weight heparins (LMWHs) are preferred over warfarin for the entire duration of anticoagulation. These recommendations are based on the studies that reported lower rates of recurrent VTE among patients treated with LMWHs for 3-6 months (7-10%) as compared to treatment with warfarin (16- 21%)15. Therefore, warfarin should be used for the treatment of VTE in cancer patients only when LMWHs are contraindicated, such as impaired kidney function. Other situations where warfarin is usually used include instances where patients prefer an oral drug to the injections despite the added benefit with LMWH and in cases where patients cannot afford the cost of LMWH therapy.

How do we treat VTE in cancer patients?

The recommended duration of treatment is at least 3 months for most forms of VTE. However, the cancer patient is at increased risk for thrombosis for many reasons as discussed earlier. Therefore, it is recommended that anticoagulation be continued for at least 6 months15 in cancer patients with VTE. In addition, continuation of anticoagulation for longer than 6 months should be considered in patients who have active cancer and/or are undergoing treatment with chemotherapy. However, clinical trials have demonstrated that the dose of anticoagulation can be safely reduced by about 30% after the first 6 weeks of treatment.

Thromboprophylaxis (clot prevention) in cancer patients

Should all cancer patients receive anticoagulation to prevent VTE?

This is a fair question given everything that has been discussed about the risk for VTE in cancer. The evidence supporting the use of UFH or LMWH for prevention of VTE in patients with cancer is stronger for certain situations compared to others. Perhaps the most important distinction is whether the patient is hospitalized or not (i.e. is ambulatory). There is convincing evidence that thromboprohylaxis in the post-surgical period is beneficial in all cancer patients undergoing surgery. Current treatment guidelines therefore recommend that all cancer patients receive thromboprophylaxis with low dose UFH or LMWH for at least 7 to 10 days following surgery lasting longer than 30 mins. In addition, patients undergoing major abdominal surgery and in those with high-risk features, such as residual tumor post surgery, coexisting obesity, and past history of VTE, extended thromboprophylaxis for up to 4 weeks is recommended15. The evidence for routine thromboprophylaxis in hospitalized, nonsurgical patients is not as strong. Clinical trials have found that routine thromboprophylaxis in all hospitalized patients is beneficial and a small number of patients in these trials had cancer. Based on these results, it is recommended that all hospitalized cancer patients receive thromboprohylaxis unless there is a contraindication for doing so, or the risk for bleeding is significant. Finally, thromboprophylaxis is not recommended in non-hospitalized (ambulatory) patients except in certain special situations, such as patients with myeloma who are treated with dexamethasone and thalidomide or lenalidomide. Additional clinical trials are underway to determine whether the benefit of thromboprophylaxis justifies the risk (and cost) in certain high risk ambulatory patient groups receiving other forms of chemotherapy.

VTE risk associated with hormone therapy

Hormonal therapy plays an important role in the treatment of patients with breast cancer. The drugs commonly used include Tamoxifen, an anti-estrogen that has weak estrogen-like effects, and aromatase inhibitors (e.g. Anastrozole or Arimidex®), a group of drugs that inhibit the synthesis of estrogen.

The risk for VTE associated with Tamoxifen among healthy women is similar to that associated with estrogen use – 2 to 3 fold higher risk. When Tamoxifen is used for treatment of breast cancer (following surgery or radiation), the VTE risk is about 1.5 to 7 fold higher than the general population16. In addition, increasing age also factors into this risk and postmenopausal women have a higher risk compared to premenopausal women. Finally, the risk with Tamoxifen is greatest when it is used concurrently with chemotherapy, where it is about 20 fold higher than the risk in the age matched general population16. The data on VTE risk associated with aromatase inhibitors are less extensive compared to Tamoxifen. In the ATAC trial (Arimidex® and Tamoxifen, Alone or in Combination), Arimidex® was associated with a lower VTE risk compared to Tamoxifen17. However, the incidence of VTE associated with Arimidex® was still greater than that in healthy women, at about 1% per year.

At present, women who are on therapy with Tamoxifen or an aromatase inhibitor, do not need to receive routine thromboprophylaxis. However, the optimal management of high risk patients, such as those with past history of VTE, remains unclear and should be assessed on a case by case basis.

Risk associated with Erythropoietin Stimulating Agents (ESAs)

ESA are agents that are similar to erythropoietin, a hormone synthesized in the kidney, which stimulates the bone marrow production of red blood cells. ESAs are used to treat cancer and chemotherapy associated anemia. A recent study found that ESAs (epoetin and darbepoetin) significantly decreased the need for red blood cell transfusions in cancer patients. However, these agents were associated with a small increase in the risk for VTE18. While concurrent thromboprophylaxis with the use of ESAs is not recommended, care must be taken when treating cancer patients already at high risk for VTE with these agents.

Biomarkers of thrombotic risk in cancer

Is there a way to identify cancer patients that are at highest risk for VTE so that VTE can be prevented in this high risk group?

Identification of clinical risk factors and laboratory markers that can reliably identify cancer patients at high risk for VTE could lead to the institution of preventive measures, such as thromboprophylaxis. Along these lines, a number of clinical risk factors are already known and these are outlined in Table 1. A number of laboratory findings have also been associated with

risk for VTE in cancer patients. These include an elevated platelet count, elevated white blood cell count, tissue factor expression in cancer cells and plasma tissue factor levels, and increase in coagulation markers (e.g. D-dimers). A risk assessment model for VTE in cancer was recently developed. This model includes a number of clinical risk factors and laboratory markers and uses a scoring system to estimate risk19. Clinical studies further expanding this model are currently underway and these efforts could lead to better identification of cancer patients at greatest risk for VTE in the near future.

Table 1: Risk factors for VTE in cancer

General risk factors
a) Age
b) Race
c) Obesity
d) History of VTE
e) Coexisting medical problems
f) Inherited and acquired thrombophilias

Cancer specific risk factors
a) Site of cancer
b) Stage of cancer
c) Type of chemotherapy (see figure 1)
d) Surgery

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