

# **Prevention of venous thromboembolism in cancer patients**

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Venous thromboembolism (VTE) is an important cause of morbidity and mortality in patients with cancer. It occurs in up to 20% of patients with an overt malignancy and is the second leading cause of death in these patients.(1)

Complex cancer- and treatment-related symptoms can mask VTE symptoms, leading to atypical presentations, such as progressive dyspnoea. Therefore, clinicians should have a low threshold of suspicion for both deep venous thrombosis (DVT) and pulmonary embolism (PE) in any patient with cancer.

VTE can also precede the diagnosis of cancer by many months; therefore, any unprovoked VTE in someone over 40 years of age should prompt investigations into the possibility of an occult malignancy.(2)

## **Hypercoagulable state**

VTE is the most common thrombotic condition associated with malignancy, but others can occur: marantic endocarditis, disseminated intravascular coagulation, arterial thrombosis, thrombotic microangiopathy and migratory superficial thrombophlebitis are all described. There is general agreement that patients with cancer are in a hypercoagulable state.

Virchow's triad suggests that VTE occurs because of three factors: alteration in blood flow, vascular endothelial injury and alteration in the constituents of the blood. Turbulent blood flow can occur because of extrinsic compression from malignant tumours or intrinsic devices, such as central venous catheters. Vascular endothelial injury can be induced by systemic anticancer therapies. The prothrombotic effect of antiangiogenic agents, such as bevacizumab and thalidomide, are particularly high. Procoagulants released from cancer and normal cells along with a decrease in natural coagulation inhibitors (reduced levels of proteins C and S) and increased platelet activation can also contribute.(3)

Certain types of cancer confer a particularly high risk such as cancers of the pancreas, brain and liver, in addition to multiple myeloma, are cited as having the highest incidence.

Patients with cancer might also share many of the factors that predispose non cancer patients to VTE.(4)

Cancer-related risk factors that predispose to venous thromboembolism : Primary site of cancer, Extensive disease,

Systemic anticancer therapy (chemotherapy, novel agents or hormonal manipulation), Presence of central venous catheter,

Steroid treatment, Recent surgery, Haematological abnormalities (high platelet count, low haemoglobin or high white cell count), Time after initial diagnosis (first 6 months are highest risk).(5)

Patient-related risk factors that predispose to venous thromboembolism : Raised body mass index, Reduced mobility, Comorbidities (respiratory disease and/or renal disease), Old age, Previous history of venous thromboembolism, Sepsis, Ethnicity (increased in those of black African descent).(5)

### **Primary Prevention Guideline Update**

Despite clearly defined risk factors for VTE in malignancy, there are insufficient data to support pharmacological VTE prophylaxis in ambulant patients with cancer. This is reflected in both national and international guidelines(American Society of Clinical Oncology Clinical Practice Guideline Update) , where primary prophylaxis is not recommended because of the lack of significant impact on patient survival.(3,6,7) Patients with multiple myeloma who are receiving thalidomide and/or lenalidomide-based chemotherapy and/or dexamethasone regimens are the exception to this rule. Their risk of serious thromboembolic events (acute cardiovascular event or sudden death) is 5–8.2% during the first 6 months of treatment; therefore, primary prophylaxis with aspirin, warfarin or LMWH is recommended.(8)

Once hospitalised, primary prophylaxis is advisable because of the high risk of VTE in immobile patients.As a result, pharmacological prophylaxis with LMWH, UFH or fondaparinux is indicated.(3,5)

Data are inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion.(9)

Patients with cancer undergoing major surgery should also ideally receive primary prophylaxis starting preoperatively and continuing for up to 7–10 days postoperatively.(3,7). Mechanical thromboprophylaxis alone is felt to be insufficient for patients with cancer and is used in cases where pharmacological measures are not possible. For those patients undergoing major abdominal or pelvic surgery, extended pharmacological prophylaxis is indicated for up to 4 weeks postoperatively because of the prolonged high incidence of VTE.(10)

LMWH is recommended for the initial 5 to 10 days of treatment of established deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis for at least 6 months.(11)

Patients with cancer should be periodically assessed for VTE risk. And oncology professionals should educate patients about the signs and symptoms of VTE.(11)

### **Novel oral anticoagulants vs heparin**

Heparins exert a variety of antithrombotic effects that are not shared by VKAs and may be of significance in preventing recurrent VTE in the cancer patient [12, 13]. These effects of heparin products include decreased binding of L- and P-selectins to their ligands, release of tissue factor pathway inhibitor, and neutralization of various cytokines and chemokines that may modulate the prothrombotic effects of malignancy. The relative role that these mechanisms play in the anticoagulant effects of heparins in malignancy is not currently known. As these mechanisms are not known to be shared by the NOACs, it is unclear whether the NOACs will have the same efficacy in cancer patients with VTE as do heparin products. [13].

New oral anticoagulants (NOACs) are now available that offer increased options for anticoagulation beyond the traditional vitamin K antagonists and low molecular weight heparins that have long been the cornerstone of treatment, three NOACs that are currently approved for use in the U.S.: the direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors, apixaban and rivaroxaban. Oncologists are likely to encounter an increasing number of patients taking these agents at the time of their cancer diagnosis or to have patients who develop indications for anticoagulation during the course of their disease. (14)

The simplicity of oral administration without need for laboratory monitoring makes the new oral anticoagulants (NOACs) an attractive option for the prevention and management of thrombotic disorders. The increased baseline thrombotic and bleeding risk of cancer patients, their propensity to develop sudden changes in renal or hepatic function, and the lack of reliable reversal strategies for the NOACs raise concerns about the use of these agents in this high-risk group.(14). Many chemotherapeutic agents have significant interactions with the CYP3A4 enzyme and/or P-glycoprotein transporter, which can alter the level of anticoagulation of the NOACs and predispose to bleeding or thrombotic complications.

The increased risk of bleeding in patients with active malignancy also raises concerns about the safety of the NOACs in this population. Cancer patients are at 2- to 6-fold higher risk for bleeding events while on anticoagulation [15, 16]. Oncology patients determined to have the highest risk for VTE and have also been found to have the highest bleeding risk [17].

Factors increasing bleeding risk in cancer patients include surgery, tissue damage from radiation, mucosal bleeding from visceral malignancies (e.g., hemoptysis with lung cancer, gastrointestinal bleeding with gastric or colon cancer, hematuria with bladder cancer, etc.), thrombocytopenia from myelosuppressive chemotherapy, the presence of the above risk factors in the cancer patient may offset these decreased bleeding rates also, Age over 75 years is a risk factor for bleeding in the anticoagulated general population, whether the anticoagulant is warfarin, LMWH, or a NOAC [18–20].

The risks and benefits of anticoagulation as well as the type of agent used need to be weighed for any patient starting anticoagulation, yet for those with malignancy the magnitude of risk is often greater than in the general population.(14)

Consideration of the use of a NOAC makes this evaluation even more complex. The following are factors that need to be considered when prescribing any anticoagulant in a patient with cancer, with some factors unique to the NOACs which are: Patient assessment ,Risk factors for bleeding ,No major bleeding events in the past 2 months ,Absence of intracranial or visceral tumor at high risk for major bleeding ,Platelet count .50,000 per mL, No anticipated decrease due to disease or chemotherapy,

Coagulation studies(Normal PT, PTT, and fibrinogen),Liver function tests(No significant hepatic impairment (e.g., Child-Pugh B or C,cirrhosis),Renal function:CrCl .30 mL/min (rivaroxaban) CrCl .15 mL/min (dabigatran and apixaban) , No anticipated fluctuations due to nephrotoxic chemotherapy or other drugs, No concomitant use of drugs with strong effect on CYP3A4 and/ or P-glycoprotein.(14)

In absence of safety and efficacy data of the NOACs in cancer populations, these agents is not currently recommended for patients with malignancy and VTE and should be used with caution in patients with active malignancy only after careful evaluation of the risks and benefits for individual patients.(14)

### **Treatment and secondary prevention of venous thromboembolism in cancer**

In those cancer patients with active disease getting chemotherapy who present with a new VTE event, a parenteral agent, such as LMWH or fondaparinux, is first-line therapy and should be continued for at least 3–6months if possible.After this time point many decisions are required, including duration of anticoagulant therapy and choice of anticoagulant. Many guidelines exist to aid in decision making regarding duration of anticoagulation and anticoagulant choice for extended treatment of VTE in cancer patients based on expert and consensus opinion [21, 22, 23].

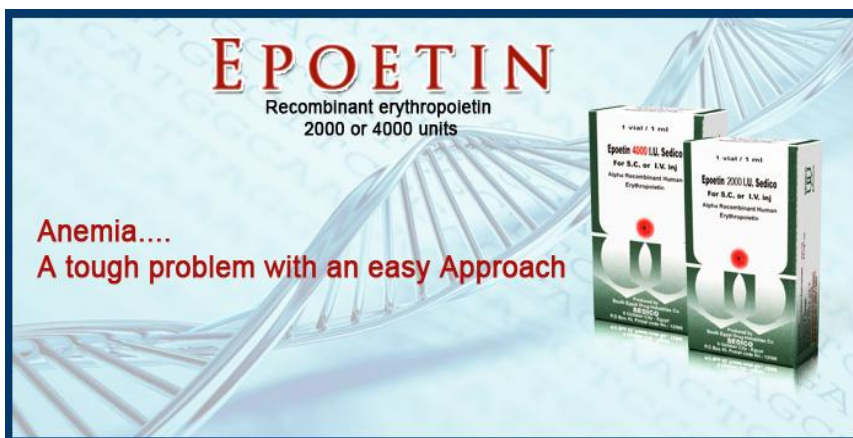
It is generally accepted that the majority of patients with metastatic disease and history of VTE should remain on anticoagulation indefinitely, but management of patients in remission after 3–6 months of anticoagulation for a VTE with no other VTE risk factors has not been studied.(14)

For some cancer patients, use of a parenteral agent is not possible. VKAs may be used with careful INR monitoring, especially if the patient is not being treated with chemotherapy that affects VKA metabolism. Rivaroxaban, the only NOAC currently FDA-approved for treatment of VTE, can be considered in select patients.(14)

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# **EXPRESSION OF GLUCOCORTICOID RECEPTOR ISOFORM IN IMMUNE THROMBOCYTOPENIA**

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## **Background:**

Glucocorticoids (GCs) are a mainstay and the most effective treatment for patients with immune thrombocytopenia (ITP). However, GC resistance has been demonstrated in nearly 30 % of ITP patients even managed with high dosages of GCs. An insight into the molecular mechanisms underlying GC resistance is important to avoid treatment with GCs in those patients who will not benefit from its use. The biological effects of GC are mainly mediated through the activation of glucocorticoid receptors (GR), forming a GC–GR complex that binds DNA to regulate gene transcription.

## **Aim Of Work**

To determine the expression of glucocorticoid receptor isoforms alpha, GR $\beta$ , GR $\gamma$ , GR $\mu$ mRNA in adult immune thrombocytopenia and its relation with glucocorticoid resistance

## **Materials and methods**

35 patients diagnosed as ITP were selected from the outpatient clinic of Hematology Department, Alexandria University Main Hospital. Cases were further sub divided into two groups according to their response to steroid (sensitive: PLT $\geq$ 30 $\times$ 10<sup>9</sup>/L, 19 patients; resistant: PLT $<$ 30 $\times$  10<sup>9</sup>/L, 14 patients) after 4 weeks treatment. Group B- consisted of 15 healthy volunteers matched for age. Pregnant, chronic infections especially HCV and H. pylori, or svstemic lupus erythromatosus were excluded. There were no history of glucocorticoid and immunosuppressive agent use by any of the patients and healthy volunteers 2 weeks prior to the study.

## **Results**

The mean age of patients in GC sensitive group was 33.4 $\pm$ 11.6, 38.1 $\pm$ 12.3in GC resistant and 31.7 $\pm$ 5.8 in controls. All the studied patients were females except for 5 males in GC sensitive group and 7 males in the controls. Our data revealed statistically significant difference between glucocorticoid receptor isoform GR  $\mu$ m RNA and GR $\alpha$ /GR $\beta$  ratio between GC resistant and GC responsive group while GR alpha, GR $\gamma$ , GR $\beta$  was insignificantly differed between groups

## **Conclusion:**

Study of glucocorticoid receptor isoforms especially GR $\mu$  and GR $\alpha$ /GR $\beta$  ratiomay be of value in determining glucocorticoid resistance before starting therapy. However further studies on a wider scale are still needed to confirm these findings,