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Venous thromboembolism in cancer patients

Kanser hastalarında venöz tromboembolizm

Mehmet Fuat Eren*, Birsen Yücel, Sadettin Kılıçkap

Department of Radiation Oncology (Assist. Prof. M. F. Eren, MD, Assist. Prof. B. Yücel, MD), Tıbbi Onkoloji Bilim Dalı (Assoc. Prof. S. Kılıçkap, MD), Cumhuriyet University School of Medicine, TR-58140 Sivas

Abstract

Venous thromboembolism (VTE) is a major complication of cancer and represents an important cause of morbidity and mortality. The incidence of VTE is 0.6-7.8%in patients with cancer more than double the incidence of VTE in patients without cancer. The risk of VTE which includes deep venous thrombosis (DVT) and pulmonary embolism (PE) is increased two to seven fold in patients with cancer. VTE risk is especially high among certain groups such as hospitalized patients with cancer and those receiving active antineoplastic therapy. Also cancer patients, who undergoing major surgery, are increased risk of VTE. Trauma, long-haul travel, increased age, obesity, previous VTE and genetic component are also predisposing factors for VTE. Patients with cancer who develop VTE should be managed multidisciplinary treatment guidelines. The primary goal of thromboprophylaxis in patients with cancer is to prevent VTE. The large majority of cancer patients should be treated with therapeutic doses of unfractioned heparin (UFH) or low molecular weight heparin (LMWH). Prophylaxis should include cancer patients who underwent major surgery for cancer and patients with a history of VTE.

Keywords: Venous thromboembolism, cancer, anticoagulation, chemotherapy, low molecular weight heparin

Özet

Venöz tromboembolizm (VTE) kanser hastalığının major komplikasyonu, morbidite ve mortalitenin en önemli nedenidir. Kanser hastalarında VTE insidansı %0,6-7,8 olup, kanser olmayan hastalardaki VTE insidansından 2 kat daha fazladır. Kanser hastalarında VTE görülme riski, buna derin ven trombozu ve pulmoner embolism de eklendiğinde 2-7 kat arası artmaktadır. VTE riski özellikle hastanede yatan kanser hastalarında ve antineoplastik tedavi alanlarda yüksektir. Bununla beraber büyük cerrahi operasyon geçiren hastalarda da VTE riski artmaktadır. Travma, uzun sureli yolculuk, ileri yaş, obezite, önceden geçirilmiş VTE ve genetik gibi faktörler VTE için predispozan faktörlerdendir. Kanser hastalarındaki tromboproflaksideki primer amaç VTE gelişmesini önlemektir. Kanser hastalarının büyük bir çoğunluğu fraksiyone olmayan heparin ve düşük molekül ağırlıklı heparin ile tedavi edilmelidir. Büyük cerrahi operasyon geçiren kanser hastalarında proflaksi yapılmalıdır.

Anahtar sözcükler: Venöz tromboembolizm, kanser, antikoagulasyon, kemoterapi, düşük molekül ağırlıklı heparin

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***Corresponding Author:**

Dr. Mehmet Fuat Eren, Radyasyon Onkolojisi Bilim Dalı, Cumhuriyet Üniversitesi Tıp Fakültesi, TR-58140 Sivas. E-mail: drmehmeteren@gmail.com

Introduction

Venous thromboembolism (VTE) is a major complication of cancer and represents an important cause of morbidity and mortality. The association of VTE with cancer was first described in 1865 by Armand Trousseau [1]. A thrombus goes on to occlude a blood vessel is known as a VTE. The incidence of VTE is 0.6-7.8% in patients with cancer

more than double the incidence of VTE in patients without cancer [2]. The risk of VTE which includes deep venous thrombosis (DVT) and pulmonary embolism (PE) is increased two to seven fold in patients with cancer [2]. Approximately 15-20 % of all VTE cases occurs in patients with cancer [1-3]. Although VTE is one of the leading causes of death among cancer patients, it is preventable disease with multidisciplinary treatment. VTE risk is especially high among certain groups such as hospitalized patients with cancer and those receiving active antineoplastic therapy. Also cancer patients, who undergoing major surgery, are increased risk of VTE. Trauma, long-haul travel, increased age, obesity, major medical illness, previous VTE and genetic component are also predispose factors for VTE. Cytotoxine chemotherapy regimens, hormone therapy (tamoxifen) or oral contraceptive agents and antiangiogenic (bevasizumab) agents are the factors with increased VTE risk. In this review, we will discuss risk stratification models that have been specifically developed to identify cancer patients at high risk for VTE and therefore might be useful in future studies designed to determine the potential benefit of primary thromboprophylaxis.

Clinical risk factors:

The incidence of VTE depends on several factors including procoagulant agents secreted by tumor cells, immobilization, surgery, central venous catheters, and systemic treatment (including chemotherapy), contribute to an increased risk of VTE in cancer patients. These factors can be grouped into 3 general categories (Table 1).

1. Patient related factors (age, ethnicity, gender, etc)
2. Cancer related factors (specific sites of cancer include the pancreas, stomach, brain, ovary, kidney, lung, hematologic malignancies, myeloma, non-hodgkin lymphoma and Hodgkin disease, cancer type and stage etc)
3. Treatment related factors (surgery, chemotherapy, anti-angiogenic agents, etc)

Table 1. Risk factors for VTE in patients with cancer.

Category	Risk factors
Patient characteristics	-advanced age -gender -ethnicity -obesity -immobility -trauma -pregnancy/postpartum -history of VTE
Cancer-related factors	-cancer site -brain -pancreas -kidney -stomach -bladder -gynecologic(uterus, ovary) -lung -testis -myeloma -non-Hodgkin lymphoma -hodgkin disease
Treatment-related factors	-major surgery -hospitalization -CVAD -chemotherapy (cisplatin) -hormonal therapy (tamoxifen, anti-eostrogens, progestins) -antiangiogenic agents (bevacizumab, thalidomide and lenalidomide) erythropiesis- stimulating agents -dehydration -infection

The rate of VTE is consistently higher in patients with cancer of the pancreas, stomach, brain, kidney, uterus, lung or ovary. Among the haematological malignancies, lymphoma and myeloma disease were reported to have the highest rates of VTE [1]. Non-surgical anticancer treatment strategies are also related with a high incidence of VTE. Chemotherapy, hormonal therapy, antiangiogenic agents, and combination regimens all have a prothrombotic effect in cancer patients.

Cancer is the cause of approximately 15-20% of the VTE cases [3]. VTE risk in solid tumor cancer patients with distant metastasis is higher than cancer patients without metastasis [4]. In retrospective studies the risk of VTE patients with metastatic breast cancer are higher than patients with localized disease [5]. Also adenocarcinomas appear to be associated with a higher risk than squamous cell cancer.

In retrospective studies, it was shown that chemotherapy was associated with a 6.5 fold increased risk of VTE [3-7]. Pre-chemotherapy thrombocytosis, leukocytosis, and hemoglobin level<10 gr/dl are predisposing factors of VTE in patients receiving chemotherapy. Cytotoxine chemotherapy regimens, hormone therapy (tamoxifen) or oral contraceptive agents and antiangiogenic (bevasizumab) agents are the factors with increased VTE risk [8, 9]. Chemotherapy with bevasizumab significantly increased risk of VTE in cancer patients [10, 11]. In the therapy of multiple myeloma, agents such as thalidomide or lenalidomide combined with high dose dexametasone, and doxorubicin are factors related with an increased risk of VTE [12]. The pathophysiolgy of thrombosis in these agents have not been illuminated, but endothelial dysfunction or deregulation of cytokine activity has been proposed as mechanisms. In addition the presence of central venous access device (CVAD) is the treatment related risk factors for VTE and it depends on the result of venous stasis and vessel injury [13, 14].

Diagnosis

The initial diagnostic work-up of all patients with suspected VTE should carry out the following tests: Medical history and physical examination, complete blood count, prothrombin time (PT), activated partial thrombolastin time (aPTT), serum biochemistry includes serum creatinine, chest X-ray, urological visit for men and gynecological visit for women. Duplex venous ultrasonography is recommended as the preferred venous imaging method for initial diagnosis of DVT. In cases of negative or undefined ultrasound results and a continued high clinical suspicion of DVT other imaging modalities such as contrast -enhanced computed tomography (CT), magnetic resonance imaging (MRI; MR venography) are recommended [15, 16].

Treatment

Patients with cancer have multiple risk factors for thromboembolic disease so the treatment of thromboembolic complications remains a difficult clinical challenge for these patients. Patients with cancer who develop VTE should be managed multidisciplinary treatment guidelines. The national comprehensive cancer network and other professional organizations have developed guidelines for VTE prophylaxis and treatment in patients with cancer. In these guidelines, the primary goal of thromboprophylaxis in patients with cancer is to prevent VTE. The large majority of cancer patients should be treated with therapeutic doses of unfractioned heparin (UFH) or low molecular weight heparin (LMWH).

UFH has short half life and allows for rapid reversal of anticoagulation in patients. UFH is generally used for VTE prophylaxis (low dose) and by intravenous infusion for treatment of VTE. Low dose UFH (5000 units) administered 3 times/day (every 8 hours) is recommended for VTE prophylaxis in cancer patients and general surgery patients [17]. Initial dosing of UFH in the treatment of VTE is weight based with a recommended regimen of 80 units/kg bolus followed by 18 units/kg per hour infusion [18]. Creatinine clearance must be < 30 mL/min in these patients. The current evidence was showed that fully reversible UFH may be preferable in unstable, complicated, hospitalized patients with a higher risk of bleeding [19].

LMWH has longer plasma half life, an improved subcutaneous bioavailability. LMWH is safe and effective for the long- term treatment of VTE in patients with cancer. Control of the international normalized ratio (INR) is difficult for patients in cancer so LMWH may be a useful treatment for these patients. Treatment with LMWH is preferred in cancer patients with established VTE for initial 5 to 10 days of treatment and should be given up to 6 months or longer to prevent VTE recurrence. Also LMWH as monotherapy is recommended for the treatment of proximal DVT or PE and the prevention of recurrent VTE in patients with advanced disease or metastatic cancer.

LMWHs such as enoxaparin, dalteparin and tinzaparin. Tinzaparin and dalteparin are equivalent efficacy and safety in the treatment of DVT, PE and recurrence of VTE [20]. Also tinzaparin is useful of immediate VTE treatment and dalteparin is useful for VTE prophylaxis [21, 22]. Enoxaparin is approved in the treatment of prophylaxis and immediate treatment of VTE. The ENOXACAN II study has shown that prolonging the standard 1-week regimen of the LMWH enoxaparin to 4 weeks may further reduce the incidence of postoperative VTE and also shown potential benefits in the secondary prevention of VTE and the reduction of bleeding complications [23]. Enoxaparin is recommended 30 mg subcutaneous daily for VTE prophylaxis and 1 mg/kg subcutaneous every 24 hour for VTE treatment for patients with creatinin clearance < 30 mL/min [23, 24].

Warfarin is an option for long term treatment of VTE in cancer patients. It should be administered concomitantly with UFH and LMWH for at least 5 days and until an INR of 2. Cancer patients with DVT should be treated for 3-6 months and PE should be treated 6-12 months with either a LMWH or warfarin. Prophylaxis should include cancer patients who underwent major surgery for cancer and patients with a history of VTE [15, 16, 24].

In conclusion; thrombosis is an important cause of morbidity and mortality in cancer patients. Multifactorial and includes demo-graphic, cancer-associated, and treatment-related risk factors for VTE in cancer patients have been identified. Effective VTE prophylaxis for cancer patients at significant risk of thrombosis reduces the VTE. All current guidelines recommend that all patients hospitalized for cancer should be considered for VTE prophylaxis in the presence of contraindications to anticoagulant therapy. LMWH is quickly and frequently therapeutic, an important concern in the treatment of VTE for these patients. A benefit has not verified at ambulatory cancer patients. It should not be forgotten that VTE is preventable disease if we treat it at right time.

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