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Cancer and Thrombosis

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Abstract: Venous thrombosis development is the most important causes of morbidity and mortality in the cases with carcinoma. Besides prevention and treatment of the disease, studies clarifying pathophysiology are required in clinical studies. It is possible to research the initiating factors of forming thrombus in two groups; intravenous and extravenous. Intravenous factors: tissue factors, carcinoma procoagulant, TNF secreted from carcerous cells, IL1, plasminogen activator inhibitor, mucin, thrombomodulus, ADP, heparin sulphat, annexing II can be considered. Extravenous factors are the size of cancerous mass, histopathologic diagnoses, the pressure it causes, vascular wall damage, venous stasis, lengthened immobilization, chemotherapy and surgical interventions. By supporting these factors that contribute to forming thrombosis in the cancer patients with the literature data, treatment choices against the risk of thrombosis will be suggested with the help of guides.

Key words: Cancer · Thrombosis · Deep venous thrombosis · Venous thromboembolysm

INTRODUCTION

The words 'cancer' and 'thrombosis' were first used by Armand Trousseau at a conference called "Phlegmasia Alba Dolens" in 1865. [1] Dr.Trousseau attributed high thrombosis incidence in the cancer patients to "spontaneous intravascular coagulation". As an irony of fate, he died of gastric cancer in a few months after he had established the similar finding developed in his left leg the same diagnosis in 1867. Billroth revived in 1878 that the susceptibility of thrombosis in cancer cases might be secondary to tumor metastasis since tumor cells often occurred in the circulating coagulum [2]. In 1938, Sproule established significant increase in the venous and arterial thrombosis incidence in various cancer cases and especially in the autopsy of the cases with pancreatic cancer [3]. After 1952, it was emphasized that superficial and deep venous thrombosis (DVT) could be one of the initial symptoms that might occur in the furtive cancer. After this first observation; many various clinical, pathological and laboratory studies performed on cancer patients have established that caogulation system can be active locally or systemically in almost every tumor cases [4,5]. The cancer organizations especially NCCN, ESMO have supported the studies on the thrombosis development during cancer disease and its cure in recent years. The Fundamental Research in Oncology and Thrombosis group have established in the frontline research that 50% of the oncologic surgeons and 5% of the medical oncologists perform routine venous thromboemboly prophylaxis on their patients [6]. It has been determined in the international IMPROVE study that thromboemboly prophylaxes have been carried out on 45% of the admitted cases because of cancer disease [7]. The rate of DVT was rather high and reached up to 20% in the cases with active tumor [6-8]. In a study carried out in Denmark, cancer was established in 18% of the inpatients due to venous thromboembolysm (VTE) [9]. In the autopsy of the cancer patients, VTE was found in over 80% of the cases and VTE was the second gratest reason of deaths in cancer inpatients [10] In another retrospective study performed by Prandoni *et al.* the cases that were established with DVT because of various reasons were followed up for two years and cancer development rates were determined in these cases. Hile only in 2-3% of the cases that developed DVT due to any secondary cause, cancer was established in the first two years; this rate was 8% in idiopathic DVT and reached 20% in recurrent idiopathic DVT [11].

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Pathophysiology: We can study factors that trigger thrombosis formation in cancer patients in two groups as intravenous and extavenous.

Intravenous Factors

Endothal Damage: Endothal surface is an essential surface in preventing thrombosis formation and procoagulant/anticoagulant interaction and maintains this function with many various mechanisms.

- *"Prostacyclin"* secreted from endothelium and *"endothelium dependent relaxation factor (EDRF)"* inhibit thrombosis adhesion, activation and aggression and cause vasodilation displaying synergic effects [12,13].
- Since ADP is also an endothal cell superficial enzyme, it restricts thrombosis aggression breaking down locally produced ADP [13]
- Thrombomodulin is the endothal cell receptor of thrombus and it converts Protein C synthesized by the liver into active Protein C. Later, active Protein C restricts procoagulant activity intravenous and arterial road by inhibiting active factor V (Va) and active factor VIII (VIIIa).
- There are some proteoglycanes such as *"heparin sulphate"* on the normal endothal surface. They increase its activation adhering to ATIII just like heparin and thus, accelerate the inhibition of some coagulation factors.
- Another feature existing in the normal endothelium is the *"annexin II receptor"* and the secretion of "*tissue plasminogen activator (t-PA)"*. Annexin II receptor causes significant acceleraration in bothh plasmin generation and t-PA kinetics by tying plasminogen and t-PA. T-PA is also controlled by the plasminogen activator inhibitor secreted from endothal cellc and leucocytes [12-14].

Tissue Factor: It is a transmembrane protein and also secreted by monocyte and macrophages besides many parenchyma and connective tissue cells. It is accepted as the initial cellular trigger of coagulation rigid recognized in recent years. Tissue factor turns factor VII into active factor VII (VIIa). Tissue factor occurred in many malign cells such as adenocarcinoma, sarcoma, melanoma and neuroblastoma (14). Tissue factor level and venous thrombosis in the immunohistochemical study on 41 cases with pancreatic cancer were 4.5 times greater than the normal [15].

The Cancer Procoagulant: It has been established that it is especially in the form of 68k-Da existing in the amniotic chorionic tissues and malign cells; it requires vitamin-K to synthesiz. Cancer procoagulant was detecred especially in the large intestinal, breast, pulmonary, renal, melanoma and acute non-lymphblastic cells. It has been established that the level of cancer procoagulant is low at remission and high at relapse in the acute non-lymphblastic leukemia cells. It was observed in the the acute proyelocytic leukemia that cancer procoagulant level decreased after it was treated with ATRA [12-16]. The most essential impact mechanism of cancer procoagulant is that it actvates factor X (Xa) and initiates coagulation from the main (common) way. Mucin that is secreted by some carcinoma cells also ha procoagulant effect and activate prothrombin on the main (common) way [17,18].

Direct Effects of Tumor Cells: Tumor cells TNF-α and IL-1 trigger the adhesion and activation of leucocytes and thrombocytes increasing the adhesion molecules. Moreover, they have effects on increasing the platelet activator factor and plasminogen activator inhibitor. When platelet activator factor activity increases, thrombocytes, monocyte and neutrophile activites also increase and thet contribute to the formation of thrombosis. Increased TNF-α activity also decelerates thrombomoduline synthesis and thus, thrombosis is accelerated by restricting the inhibition of Va and VIIIa. As a result; coagulation system triggers the occurrence of thrombosis with the help of thrombocytes and leucocytes and causes thrombin generation by being active intravenous, extravenous and main (common) way [11,14-17]. It is a fact that thrombocytes also play a role in hipercoagulation. Theh have been detected in 30-60% of the thrombocytic cancer patients [15]. Thrombocyte activity increased in some clonal diseases, for instance; myeloproliferative diseases and paroxysmal nocturnal hemoglobinorrhea [5,15].

The hyperactivity of thrombocytes depends on the increased thrombine caused by tumor and ADP activity, the von Willebrand factor secreted from the injured endothel and the increase of the little membrane particles secreted from tumor cells. As the little membrane particles are especially in the phospholipid form, they facilitate thrombosis formation [16,17].

The fact that the tendency of thrombosis in cancer patients vary is closely related to how much hemostatic mechanism is active. If the level of hemostatic mechanism

activation is at minimal level, these cases usually show no symptoms and their tendency of thrombosis is only established when fibrinopeptide A level is proved to be high. Intermediate level activation in hemostatic mechanism causes venous and arterial thrombosis. If the stimulus is very severe, hemorrhage diathesis such as disseminated intravascular coagulation may occur [18].

Extravenous Factors

Surgical Procedures: It has been stated that the most considerable cause of death in the first follow-up period of the cancer patients who had major operation is venous thromboemboly [15]. Adenocarsinomas of abdominal organs (pancreas, stomach and gall tracts), small celled pulmonary cancer and myeloproliferative diseases are among the cancers that have more tendencies to thrombosis. Hemorrhage complications occur more in prostatic cancers than thrombotic complications [19,20]. The death rate was established six times greater in the cases that developed thrombosis than who did not develop thrombosis during the two-year follow-up of the gynecology oncology cases [21]. Operation length, old age, phase 3-4 cases, lengthened anaesthesia, experienced thrombosis history are the other factors triggering thrombosis following the surgical procedures [22].

Venous Stasis and Immobilization: The size of the cancer mass, its pressure on the large blood vessels and long immobility because of general conditions of the patient initiates thrombosis formation. Heitz *et al*. determined that the risk for the development of venous thrombosis was ten times greater in the cases, which underwent major operation and remained inactive for long, than those who were active in a short time [23].

Chemo and Radiotherapy Procedures: They increase the risk of thrombosis by exhibiting toxic effect on the vascular endothel in the area where chemo and radiotherapy are applied and increasing cytocine secretion. ASCO and NCCN suggested studying their medicines in their guide in three groups;

Cyctotoxic Chemoterapy Regimes: Venous thrombosis development rate was found as 10.9% in the patient group who received chemotherapy since they were diagnosed as colorectal cancer retrospectively [20] Thrombosis incidence increased by 4.7-7.2% as a result of using medicines like cyclophosphamide, methotrexate or 5FU in breast cancer treatment [22] In another series, it was established that quinary medicine combination increased thromboemboly incidence by 17.6% in the cases with phase-IV breast cancer [19]. In subsequent seven ECOG studies, 2673 breast cancer cases were grouped randomly in adjuvant chemotherapy or follow up groups and venous and arteriel thrombosis incidence were investigated. While the thrombosis risk in the follow up group was 1.6%, it increased to 5.4% in the adjuvant chemotherapy group (p=0.0002) [22-24].

Estrogen Included Hormone Therapy: While venous thrombosis risk was determined as 2.8% in the cases who underwent tamoxifen+chemotherapy during premenopausal period, this rate was 0.8% in the cases who receieved only chemotherapy (p=0.03). In the postmenopausal period, venous thrombosis risk was 8% in the chemotherapy+ tamoxifen group, 2.3% in the group that only receieved tamoxifen and 0.4% in the follow up group (p=0.03 ve p=0.001). Today it is a commonly accepted fact that tamoxifen is essential in the breast cancer prophylaxis. In P1 study, tamoxifen decreased mean 49% in breast cancer risk. However, DVT risk was 1.6% times and pulmonary emboly risk was 3 times greater in the group administrated tamoxifen in this study. [20,23-27]. Venous thrombosis risk was 20% greater in the cases administrated Diethylstilbestrolphostat +doxorubicin than those who received only doxorubicin [28].

Antiangiogenic Medicines: It is a known fact that the medicines like Thalidomide, Dexametazon, Lenalidomide, which are especially used for multiple myeloma, increase thrombosis risk of development factors used as a cancer support treatment [29-31].

Central Venous Catheter Application: Central venous catheter is a modern and indispensible treatment method in the hematology-oncology patient treatment. Among these, we can mention Hickman catheter, implantable catheter (Port-ACath) and central catheters placed through peripheric vessels. Thrombosis caused by catheter is the most important complications of central venous catheters. Thrombosis in the central catheter results from the maintanence and size of catheter, location, infection existence, the injury it causes in the vessel. For instance; thrombosis risk in the cateters with three lumens is greater than in the cathters with single or double.If the apex of the catheter is very close to superior vein or right atrium, thrombosis risk increases more.

Pulmonary emboly risk secondary to central venous catheter thrombosis is also rather high and ranges between 16-36% [33-36].

Diagnosis and Differential Diagnosis: Swelling in the upper and lower extremities, sensitivity, rush and pain are the most significant symtoms of DVT. Chest pain, shortness of breath and tachypnea are the most common symptoms encountered in pulmonary emboly. Hemoptiz is rare and occurred only in pulmonary infract cases.Abdominal pain, acit and hyperbilirubinemia is frequent in the thrombosis of intra-abdominal organs, for example; portal vein, spleenic vein and superior mesenteric vein [31,32,37,38].

D-Dimer test, Doppler ultrasound, ventilation/ perfusion scan, contrasted lung, abdomen and pelvis tomographies are the diagnostic methods. Quantitative D-Dimer tset is essential.this test is extremely sensitive and its normal level eliminates 95/98% the possibility of thrombosis. It is possible to evaluate the blood flow, vessel pressure, yhe structure of the vessel wall with stained Doppler test. It is frquently used in superficial vessels. CT or MRI are used in the cases suspected of DVT but can not be established with USG to scan especially inferior vena cava, deep pelviv artery, pulmonary vein or in the cases when using contrast substance is contraindicated [37,38]. Establishing venous thrombolism risk scores in cancer patients

The Location of Caner:

- Very high risk areas: stomach, pancreas; risk score: 2
- High risk areas: lung, lenphoma, gynecologic and genitourinary tract tumors; risk score: 1
- Low risk areas: breast, colo-rectal, head and neck; risk score: 1
- Thrombocyte is >350X10/L pre-chemotherapy; risk score: 1
- Hemoglobin level is <10gr/dl or using agents stimulating erythrophose; risk score:1
- Locoyte number is 11x109; risk score: 1
- Body mass index is >35kg/m; risk score:1

Treatment: Using anticoagulants in cancer patients is complicated since they increase the risk of hemorrhage and thrombosis. In a retrospective study, the risk of venous thrombosis occurrence in patients without canser was 4.9% and 12% in cancer patients in the 12-month follow-up [39]. In another study, hemorrhage defect was established caused by thrombocyte function failure related to heparin in the 5-10 days in one fourth of the heparinized cases [14,16,28,40].

Warfarin is a safe anticoagulant in venous and arterial thrombosis prophylaxis. The hemorrhage risk of the cancer cases who take warfarin is not considerably different from the cases without cancer. However, reiterative thrombosis risk has been found 6 times greater in these cases [11,17,19,40,41]. For instance; in a study carried on phase-IV breast cancer cases, low dose warfarin (INR 1.3-1.9) was administrated to 152 patients and venous thrombosis risk was found as 0.7% in these cases. Venous thrombosis risk was established as 4.4% in placebo group and this rate is six times higher than the warfarin group (p=0.031). It was determined in this study that low dose warfarin decreased 85% the relative thrombosis risk.However, there was no significant difference in the hemorrhage complications and mortality between both groups [27]. It should be remembered that warfarin interacts with some antibiotic (trimethoprim, sulfamethoxazole, fluxanazole), chemoterapic medicines (5FU, Capacitabine) and increases its effect [20,21,24,27,38]. Low molecular rated heparins have been used successfully for the thrombosis treatment and prophylaxis of cancer patients. Kakkar *et al.* compared reviparin sodium with standard heparin in 125 cases with cancer and thrombosis. While the response to treatment was19% in intravenous heparin+warfarin group, the response was 46.7% and 46.3% in the group receiving subcutaneous reviparin sodium+warfarin once a day (p=0.03).

Clinical recurrence rate was 17.1% in intravenous heparin+warfarin group and 3.0% and 5.9% respectively in the groups receiving subcutaneous reviparin sodium+warfarin once a day and twice a day (p=0.03). In conclusion, low molecular rated heparin *(reviparin sodium)* was proved to be more effective than standard heparin in DVT treatment of cancer cases [38,43]. In another study *(Enoxacan I)*, DVT prophylaxis followed by the abdominal and pelvic cancer surgery of 1115 cancer patients was compared with 40mg subcutaneous Enoxaparin once a day and 5000 unit subcutaneous standard heprin three times a day and thrombosis insidences were 14.7%,18.2% respectively (p>0.05). As a result; it has been emphasized that 40mg subcutaneous Enoxaparin once a day equals 5000 unit subcutaneous standard heparin [29-31,33]. Bergqvist *et al.* applied 40mg subcutaneous Enoxaparin once a day for 8±2 on 505 cases who underwent abdominal and pelvic cancer and then

radomized them into two groups in their *Enoxacan II* study. One group continued 40mg subcutaneous Enoxaparin once a day and the other group were given pacebo.

While VTE incidence was 12%in the placebo group, this rate was 4.8% in Enoxaparin group (p=0.02). Consequently, 40mg subcutaneous Enoxaparin once a day for three weeks decreased the risk of VTE 60% in the postoperative period [45]. Although oral anticoagulants have been successful in most of the cancer cases, the risk of recurrent thrombosis is high in these cases. Lee *et al.* compared oral anticoagulant (Warfarin) with another low molecular rated heparin Dalteparin. The cancer patients who developed DVT and/or pulmonary emboly were randomized into two groups. One group were given subcutaneous Dalteparin (200 IU/kg) once a day for 5-7 days + Warfarin for 6 months, the othe r group were given only subcutaneous Dalteparin (200 IU/kg for a month, 150 IU/kg for 5 months). Six months later, recurrent VTE occurred in 27 of 336 cases in the dalteparin group (9%), recurrent VTE occred in 53 of 336 cases in the oral anticoagulant (Warfarin) group (17%) (p=0.002). There was no significant difference in hemorrhage incidence and mortality [46]. ESMO has proved that if low molecular rated heparin dose initiated in the thrombosis treatment of the cancer cases continues with reduced doses, it decreases hemorrhage risk directly propotiaonally [40,41,47].

Prognosis: It has been emphasized that the thrombosis simultaneous with cancer or established within a year occurs more in advanced cancers and affects prognosis negatively. Sorenson *et al.* compared cancer prognosis in the cases with VTE determined at diagnosis and a year after diagnosis. While survival rate of the cases who had thrombosis at diagnosis was 12%, it was 36% in the control group (those who did not have thrombosis but cancer) (p=0.001). Although survival rate of the cases who developed VTE after they had been established with cancer was 38%, it was 47% in control group (p=0.001). In conclusion, it has been emphasized that the thrombosis simultaneous with cancer or established within a year occurs more in advanced cancers and affects prognosis negatively [47]. Agnelli *et al.* compared the mortality of cancer and thrombosis with the cases who took low molecular rated heparin and standard heparin. While they found the mortality rate in the cases who took standard heparin as 31%, it was 11% in the cases who took low molecular rated heparin (p=0.005) [48]. Although it is not known exactly how heparin lengthens lifetime, it is considered that it is related to angiogenesis inhibition [34,35,36,49].

CONCLUSION

VTE risk was fund rather high in malign diseases. Thrombasis in cancer patients progresses more aggressively. The etiology of thrombosis has many factors. Although warfarin seems to be an effective agent in the thromboprophylxsis of cancer patients, recurrent VTE rate is 6 times higher in these patients. Low molecular rated heparin has been found more effective than standard heparin in VTE treatment and prophylaxis. There are some reports that both Warfarin and low molecular rated heparin extends life span in some patients.

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REFERENCES

1. Aderka, D., A. Brown, A. Zelikovski and J. Pinkhas, 1986. Idiopathic deep vein thrombosis in an apparently healthy patient as a premonitory sign of occult cancer. Cancer. 57(9): 1846-1849.
2. Billroth, T., 1978. In lectures on surgical pathology and therapeutics (transl from ed 8). New Sydenham Society,
3. Sproule, E.E., 1938. Carcinoma and venous thrombosis: The frequency of association of carcinoma in the body or tail of the pancreas with multiple venous thrombosis. Am J. Cancer. 34(5): 566-570.
4. Wright, I.S., 1952. The pathogenesis and treatment of thrombosis. Circulation. 5(2): 161-188.
5. Rickles, F.R. and R.L. Edwards, 1983. Activation of blood coagulation in cancer: Trousseau's syndrome revisited. Blood. 62(1): 14-31.
6. Kakkar, A.K., M. Levine, H.M. Pinedo, 2003. *et al.* Venous thrombosis in cancer patients: insights from the FRONTLINE survey. Oncologist. 8: 381-388.
7. Tapson, V.F., H. Decousus, M. Pini, 2007. *et al.* Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. Chest. 132: 936-945.

8. Heit, J.A., W.M. O'Fallon, T.M. Petterson, C.M. Lohse, M.D. Silverstein, D.N. Mohr and L.J. Melton, 2002. 3rd. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Archives of Internal Medicine. 162(11): 1245-1248.
9. Bauer, K.A., 2000. Venous thromboembolism in malignancy [Editorial] Journal of Clinical Oncology. 18(17): 3065-3067.
10. Sorensen, H.T., L. Mellemkjaer, F.H. Steffensen, J.H. Olsen and G.L. Nielsen, 1998. The risk of a diagnosis of cancer after primary deep vein thrombosis or pulmonary embolism. New England Journal of Medicine. 338(17): 1169-1173.
11. Prandoni, P., A.W. Lensing, A. Cogo, 1996. *et al.* The long-term clinical course of acute deep venous thrombosis. Ann Intern Med., 125: 1-7.
12. Green, K.B. and R.L. Silverstein, 1996. Hypercoagulability in cancer [Review] Hematology - Oncology Clinics of North America. 10(2): 499-530.
13. Tesselaar ,M.E., F.P. Romijn, I.K. Van Der Linden, 2007. *et al.* Microparticle-associated tissue factor activity: a link between cancer and thrombosis? J. Thromb Haemost. 5(3): 520-527.
14. Davila, M., A. Amirkhosravi, E. Coll, 2008. *et al.* Tissue factor-bearing microparticles derived from tumor cells: impact on coagulation activation. J. Thromb Haemost. 6(9): 1517-1524.
15. Tesselaar, M.E., F.P. Romijn, I.K. Van der Linden, 2009. *et al.* Microparticle-associated tissue factor activity in cancer patients with and without thrombosis. J. Thromb Haemost. 7(8): 1421-1423.
16. Khorana, A.A., S.A. Ahrendt, C.K. Ryan, 2007. *et al.* Tissue factor expression, angiogenesis and thrombosis in pancreatic cancer. Clin Cancer Res., 13(10): 2870-2875.
17. Donati, M.B., A. Falanga, R. Consonni, M.G. Alessio, R. Bassan, M. Buelli, L. Borin, L. Catani, E. Pogliani, L. Gugliotta, 1990. *et al.* Cancer procoagulant in acute non lymphoid leukemia: relationship of enzyme detection to disease activity. Thrombosis & Haemostasis. 64(1): 11-16.
18. Falanga, A., L. Iacoviello, V. Evangelista, D. Belotti, R. Consonni, A. D'Orazio, L. Robba, M.B. Donati and T. Barbui, 1995. Loss of blast cell procoagulant activity and improvement of hemostatic variables in patients with acute promyelocytic leukemia administered all-trans-retinoic acid. Blood. 86(3): 1072-1081.
19. Blom, J.W., C.J. Doggen, S. Osanto and F.R. Rosendaal, 2005. Malignancies, prothrombotic mutations and the risk of venous thrombosis. JAMA. 293: 715-722.
20. Kroger, K., D. Weiland, C. Ose, 2006. *et al.* Risk factors for venous thromboembolic events in cancer patients. Ann Oncol., 17(2): 297-303.
21. Caprini, J.A., J.l. Arcelus and J.J. Reyna, 2007. Effective risk stratification of surgical and nonsurgical patients for venous thromboembolic disease. Semin Hematol. 38: 12-19.
22. Bick, R.L., 2003. Cancer-associated thrombosis. N Engl. J. Med., 349(2): 109-11.
23. Otten, H.M., J. Mathijssen, H. Ten Cate, 2004. *et al.* Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: an underestimated phenomenon. Arch. Intern Med., 164(2): 190-194.
24. Goodnough, L.T., H. Saito, A. Manni, P.K. Jones and O.H. Pearson, 1984. Increased incidence of thromboembolism in stage IV breast cancer patients treated with a five-drug chemotherapy regimen. A study of 159 patients. Cancer. 54(7): 1264-1268.
25. Andtbacka, R.H., G. Babiera, S.E. Singletary, 2006. *et al.* Incidence and prevention of venous thromboembolism in patients undergoing breast cancer surgery and treated according to clinical pathways. Ann Surg., 243: 96-101.
26. Chew, H.K., T. Wun, D.J. Harvey, 2007. *et al.* Incidence of venous thromboembolism and the impact on survival in breast cancer patients. J. Clin Oncol., 25: 70-76.
27. Fisher, B., J. Costantino, C. Redmond, 1989. *et al.* A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N. Engl. J. Med., 320: 479-484.
28. Leaf, A.N., K. Propert, C. Corcoran, 2003. *et al.* Phase III study of combined chemohormonal therapy in metastatic prostate cancer (ECOG 3882): an Eastern Cooperative Oncology Group study. Med Oncol., 20: 137-146.
29. Zangari, M., E. Siegel, B. Barlogie, 2002. *et al.* Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. Blood. 100:1168-1171.
30. Knight, R., R.J. DeLap and J.B. Zeldis, 2006. Lenalidomide and venous thrombosis in multiple myeloma. N. Engl. J. Med., 354: 2079-2080.

31. Hussein, M.A., 2006. Thromboembolism risk reduction in multiple myeloma patients with immunomodulatory drug combinations. Thrombo Haemost. 95: 924-930.
32. Moss, J.F., L.D. Wagman, D.U. Riihimaki and J.J. Terz, 1989. Central venous thrombosis related to the silastic Hlckman-Broviac catheter in an oncologic population. J. Parenter Enteral Nutr., 13: 397-400.
33. Verso, M. and G. Agnelli, 2003. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. J. Clin Oncol. 21: 3665-3675.
34. Lee, A.Y., M.N. Levine, G. Butler, *et al.* 2006. Incidence, risk factors and outcomes of catheter-related thrombosis in adult patients with cancer. J. Clin Oncol. 24: 1404-1408.
35. Linenberger, M.L., 2006. Catheter-related thrombosis: risks, diagnosis and management. J. Natl. Compr. Cane. Netw. 4: 889-901.
36. Van Rooden, C.J., E.F. Schippers, R.M. Barge, *et al.* 2005. Infectious complications of central venous catheters increase the risk of catheter-related thrombosis in hematology patients: a prospective study. J. Clin Oncol. 23: 2655-2660.
37. Kroger, K., D. Weiland, C. Ose, *et al.* 2006. Risk factors for venous thromboembolic events in cancer patients. Ann Oncol. 17: 297-303.
38. Prandoni, P., A.W. Lensing, A. Piccioli, *et al.* 2002. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 100: 3484-3488.
39. NCCN Clinical Practise Guidelines in Oncology. Venous Thromboembolic Disease V. 1.2010
40. Lyman, G.H., A.A. Khorana, A. Falanga and F. Roila, 2010. Venous Tromboembolism in cancer patient: ESMO Clinical Practise guidelines for the management. Ann Onc. 21(5): 274-276.
41. Caprini, J.A. and J.l. Arcelus, 2007. Reyna JJ. Effective risk stratification of surgical and nonsurgical patients for venous thromboembolic disease. Semin Hematol. 38: 12-19.
42. Cohen, A.T., V.F. Tapson and J.F. Bergmann, *et al.* 2008. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet. 371(9610): 387-394.
43. Kakkar, A.K., M.N. Levine, Z. Kadziola, *et al.* 2004. Low molecular weight heparin, therapy with dalteparin and survival in advanced cancer: the fragmin advanced malignancy outcomestudy (FAMOUS). J. Clin Oncol. 22: 1944-1948.
44. Superficial Thrombophlebitis Treated By Enoxaparin Study Group. A pilot randomized double-blind comparison of a low-molecular-weight heparin, a nonsteroidal anti-inflammatory agent and placebo in the treatment of superficial vein thrombosis. Arch Intern Med., 163(14): 1657-1663.
45. Bergqvist *et al.* Enoxacan II results. Heparin in cancer surgery. Proc. Am. Soc. Clin. Oncol. 27(29): 4881-4884.
46. Lee, A.Y., M.N. Levine, R.I. Baker, C. Bowden, A.K. Kakkar, M. Prins, F.R. Rickles, J.A. Julian, S. Haley, M.J. Kovacs and M. Gent, 2003. Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy forthe Prevention of Recurrent Venous Thromboembolismin Patients with Cancer (CLOT) Investigators. Lowmolecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism inpatients with cancer. N. Engl. J. Med., 349: 146-153.
47. Sorensen, H.T., L. Mellemkjaer, J.H. Olsen and J.A. Baron, 2000. Prognosis of cancers associated with venous Thromboembolism. N. Engl. J. Med., 343(25): 1846-1850.
48. Agnelli, G., 1997. Venous thromboembolism and cancer: a twoway clinical association. Thrombosis & Haemostasis. 78(1): 117-120.
49. Akl, E.A., I. Terrenato, M. Barba, *et al.* 2008. Extended perioperative thromboprophylaxis in patients with cancer. A systematic review. Thromb Haemost. 100(6): 1176-1180.