บทฟื้นฟูวิชาการ

Hypercoagulable state in malignancy

Jutharat Sutheesophon*

Sutheesophon J. Hypercoagulable state in malignancy. Chula Med J 2000 Mar; 44(3): 199 - 209

Hypercoagulable state is a not uncommon complication in malignancy. This abnormality presents in the majority of patients with metastatic disease. The occurrence of thromboembolism due to the hypercoagulable state complicates the patient's management. This abnormality is induced by 1) abnormalities in blood flow 2) abnormalities in blood composition 3) abnormalities in blood vessel walls. The use of anticancer drugs also increases the risk of thrombosis. Treatment of venous thromboembolism in cancer patients is similar to treatment of venous thromboembolism caused by other diseases, that is, anticoagulant agents, fibrinolytic agents and inferior vena caval filters.

Key words: *Hypercoagulable, Thromboembolism, Malignancy, Treatment.*

Reprint request : Sutheesophon J, Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication. November 3,1999.

*Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University

จุฑารัตน์ สุธีโสภณ. Hypercoagulable state **ในผู้ป่วยโรคมะเร็ง. จุฬาลงกรณ์เวชสาร** 2543 **มี.ค**; 44(3): 199 - 209

ภาวะ Hypercoagulable state เป็นภาวะแทรกซ้อนที่พบได้บ่อยในผู้ป่วยโรคมะเร็ง โดยเฉพาะในผู้ป่วยที่อยู่ในระยะที่มีการแพร่กระจายของโรค เป็นสาเหตุของการเกิดภาวะ Thromboembolism และ pulmonary embolism ซึ่งเป็นสาเหตุการตายของผู้ป่วยที่สำคัญ สาเหตุของการเกิดภาวะ Hypercoagulable state ในผู้ป่วยโรคมะเร็งแบ่งออกเป็น 1.) ความผิดปกติของการไหลเวียนโลหิต 2.) ความผิดปกติของสารกระตุ้นและสารต้านการแข็งตัวของเลือด และ 3.) ความผิดปกติของเส้นเลือด นอกจากนี้การเกิด Thromboembolism ยังอาจเป็นผลจากการได้รับยาต้านมะเร็งบางชนิด ในปัจจุบันการรักษาภาวะ Venous thromboembolism และป้องกันการเกิดภาวะ pulmonary embolism ในผู้ป่วยโรคมะเร็งนั้นใช้หลักการเดียวกับการรักษาภาวะ Venous thromboembolism จากสาเหตุอื่น โดยแบ่งวิธีการรักษาออกเป็นการใช้สารต้านการแข็งตัวของเลือด (Anticoagulant agents), สารละลายลิ่มเลือด (Fibrinolytic agents) และการใช้ Inferior vena cava filter ตามความเหมาะสม

Thromboembolism due to a hypercoagulable state is a not uncommon paraneoplasitic syndrome. Abnormalities of blood coagulation tests in cancer patients, which characterize the so-called "hypercoagulable state",are commonly reported, even in the absence of clinically evident thrombotic disease.[1-2] Some abnormality of blood coagulation is detectable in 50 % of cancer patients and up to 95 % of those with metastatic disease.[3,4]

These abnormalities, recognized as a complication of malignant disease, are present in the majority of patients with metastatic cancer. The occurrence of thrombosis complicates the patient's management. Thromboembolism is the major cause of morbidity and mortality in cancer patients and is related to a multitude of effects of malignancy on the hemostatic system. Many mechanisms of this complication have been postulated. Prevention and treatment of this complication is now an important part of treatment of cancer patients.

Migratory Thrombophlebitis (Trousseau's syndrome)

Migratory thrombophlebitis was first described by Armand Trousseau 130 years ago, in 1865, when he reported a high frequency of venous thrombosis in a series of patients with gastric carcinoma.[5] He concluded that this was secondary to a "special crisis in the blood" that predisposed these patients to spontaneous intravascular coagulation. Billroth[6] reported in 1878 that human tumor cells were frequently found circulating within thrombi and suggested that the pathologic process might be related to metastasis formation. In 1938, Sproule[7] reported the incidence of venous and arterial thrombosis at the post-mortem examination of patients with carcinoma of the tail and body of the pancreas. In 1952 it was restated by Wright,[8] that thromboembolic disease is often the earliest recognizable manifestation of an occult malignancy. Now, a variety of other thromboembolic disorders of the venous and arterial systems in the context of malignancy have been termed Trousseau's syndrome.

Evidence of thromboembolism is evident in almost 50% of cancer patients at post-mortem and is related to the type of malignancy. For example, thrombosis is a more common complication of pancreatic and gastric tumors than of prostate or skin cancers. In patients with mucin-producing adenocarcinoma, myeloproliferative disorders, acute promyelocytic leukemia, or brain tumors, thrombotic episodes are particularly common.[9-11] The association between cancer and thrombosis is further confirmed by the observation that there is a significantly higher incidence of occult malignancy in patients with deep vein thrombosis (DVT). Venous thromboembolism may appear before the cancer has become symptomatic and may lead to an earlier diagnosis of cancer.[12-14]

Pathogenesis of the Hypercoagulable State in Malignancy

There have been numerous pathologic,clinical, and laboratory studies that confirm both local and systemic activation of coagulation in virtually all types of malignancies. The advances in cell biology, biochemistry, and molecular biology have led to considerable insight into how cancer interacts with the hemostatic system to cause a thrombotic disorder, and it has now become clear that the hypercoagulability in cancer represents more than the effects of immobility, inanition, or venous obstruction by malignant tumors.

The pathogenesis of the hypercoagulable state,[15] induced by cancer is complex and involves the interaction of multiple factors which can be categorized as:

1. Abnormalities in Blood Flow

Comorbid conditions, frequently associated with cancer such as surgery, immobilization, bed rest, or vascular compression by the tumor masses, especially the bulky tumors, are common causes of venous stasis.[16 - 17] The venous stasis results in endothelial cell hypoxia and injury as well as delayed clearance of activated coagulation factors, thus predisposing to the development of thromboembolic diseases.[18]

2. Abnormalities in Blood Composition

The interaction between tumor cells and the coagulation system causes changes in blood composition that lead to the hypercoagulable state. These alterations are induced by:

2.1 Tumor Cell Procoagulant

Tumor cell procoagulant[19-20] can be divided into two major categories:

2.1.1 Tissue Factor (TF)

Tissue factor is a transmembrane protein expressed on normal human parenchymal and connective tissue cells and many of their malignant phenotypes, such as adenocarcinoma, sarcoma, melanoma, neuroblastoma , leukemia and lymphomas. TF is a nonproteolytic cofactor for factor VIIa in the activation of either factor IX or factor X.

2.1.2 Cancer Procoagulant (CP)

Cancer procoagulant is a cysteine protease that directly activates factor X, independently of the tissue factor/factor VIIa complex, and has been found in extracts from several human malignant tissues, as well as extracts from benign tumors.

2.2 Normal Host Tissue Response to the Tumor

2.2.1 Platelets

Thirty to 60 % of patients with malignancy have thrombocytosis and only 4 -11 % of untreated patients have thrombocytopenia.[11,21-22] Thrombocytosis, per se, does not increase the risk for thromboembolism. Functional abnormalities of platelets have been described only rarely and these were ascribed to the presence of fibrin (ogen) degradation products.[23] Increased platelet reactivity may contribute to hypercoagulability.

The mechanisms for platelet activation in malignancy are tumor-induced thrombin generation, ADP production by tumor cells, and also the elevation in plasma vWF levels which is either an acute phase reaction or is due to endothelial cell perturbation.[24-25]

2.2.2 Endothelial Cells

For endothelial cells to become procoagulant they have to be exposed to inflammatory cytokines and peptide products that are produced in response to tumor cells.[26] Tumor-induced cytokines, such as tumor necrosis factor, interleukin -1, and vascular endothelial growth factor (VEGF) are chemotactic for tumor-associated macrophages (TAMS) and/or tumor neovascular endothelial cells (VEDs), rather than (or in addition to) the tumor-cell PCA. For example, tumor necrosis factor (TNF) and Interleukin-I (IL-1) both induce an increase in endothelial cell expression of leukocyte adhesion molecules, platelet activation, tissue factors, and plasminogen activator inhibitor (PAI).TNF increases endothelial cell production of IL-1 and down-regulates thrombomodulin expression.

2.2.3 Monocytes

In cancer patients, normal host cells, particularly monocytes, can be stimulated and express procoagulant activity (PCA). Monocytes can also produce and / or assemble coagulation factors on their plasma membrane surface, as well as bind fibrinogen.[26] Monocytes / tissue macrophages are found infiltrating experimental and human tumors and may become activated either directly by tumor-specific antigens, immune complexes involving tumor antigens, or tumor- associated proteases, or indirectly by cytokines secreted by other immune cells in response to tumor-related antigens.[14] In addition, activated monocytes / macrophages stimulate the production of a variety of cytokines such as IL-1 and TNF which also induce coagulation.

2.3 Hepatic Dysfunction and Effects on Naturally Occurring Anticoagulants

Hepatic dysfunction due to tumor involvement is common in cancer patients, and it may cause abnormalities of the hemostatic system. Multivariate analysis has shown that both thrombotic and hemorrhagic complications are due to decreased hepatic synthesis of both anticoagulant and procoagulant proteins.[14,27 - 28] Antithrombin-III (AT-III) and Protein - C (PRC) are two major natural anticoagulants produced by the liver.[29 - 30] AT-III is the main inhibitor of thrombin. Protein - C is a potent inhibitor of activated Factors V and VIII. [31] Many studies suggest that the synthesis of these anticoagulants is decreased in metastatic disease. Honegger and colleaques showed that AT-III levels were low in patients with colon cancer, ovarian cancer, and prostate carcinoma. The level was lower in patients with metastatic disease. Nand and colleague confirmed that, in patients with solid tumors, 71% had low Protein-C (PRC) levels at the time of diagnosis.

2.4 Plasminogen Activator

Plasminogen activator (PA) is a serine protease secreted by most tumors.[23] PA generates local proteolytic activity which may help the tumor cells overcome the natural barrier of the vascular basement membrane and disseminate.[32 - 33] The amount of fibrin correlates inversely with the plasminogen activator. The plasminogen activator produced by tumors initiates the proteolytic cascade, and appears essential for the invasion of the tumor cells into the vascular lumen.[34] Inhibition of the PA pathway has been shown to reduce the metastatic potential in experimental systems using human tumor cell lines.

3. Abnormalities in Blood Vessel Walls

Tumor cells induce the endothelial procoagulant by:

1) Cytokines and/or tumor products released in reaction to the tumor

2) Tumor extension from extrinsic sites

3) Direct tumor invasion into the vascular space

4) Tumor cells also release a vascular permeability factor (VPF), which increases microvascular permeability and leads to extravascular accumulation of fibrinogen and other plasma-clotting proteins. This factor is probably crucial for the extravascular fibrin/fibrinogen deposition seen in and around tumors.[14]

The Anti-cancer Drugs Increase the Thrombotic Risk in Cancer Patients

Venous thromboembolisms have been

observed to occur with increased frequency in women receiving multiagent chemotherapy for stage II and stage IV breast cancer.[35-36] Both venous and arterial thrombotic events have been reported in patients undergoing hormonal and chemo-hormonal adjuvant therapy.[37] The ECOG study which reviewed adjuvant therapy in breast cancer for the occurence of vascular complications showed that the frequency of thrombosis, both venous and arterial thrombi, was 5.4 % among patients who received adjuvant therapy and 1.6% among patients under observation.[38] The anti-cancer drug increases the thrombotic risk. The postulated mechanisms for anti-cancer drug-related thrombosis are:

1) The release of procoagulants and cytokines from the damaged cells

2) The direct drug toxicity on the vascular endothelium

3) The direct induction of monocytes or tumor cell tissue factors by chemotherapeutic agents

4) The decrease in physiological anticoagulants.[39]

Special Clinical Manifestations of Thromboembolism in Cancer Patients Thrombophlebitis

A thrombus usually involves the extremities or the viscera.[40] The phlebitis is often migratory and recurrent, involving one vein group first and then improving, only to involve another vein group soon thereafter. Sometimes several vein groups are involved simultaneously. The superficial as well as deep veins may be involved. The severe forms of ischemic phlebitis, including venous gangrene and phlegmasia cerulea dolens, are also often associated with underlying malignancies.[41]

Thrombotic endocarditis :

Non-bacterial thrombotic endocarditis

Marantic endocarditis

Non-bacterial thrombotic endocarditis (NBTE) is characterized by the presence of noninfectious thrombotic vegetations on cardiac valves and is usually associated with mucin-producing adenocarcinomas.[42] These lesions result from fibrin and platelet deposition on the walls of the valves. Aortic and mitral valves are involved in almost equal numbers in patients, and bivalvular involvement has been noted in approximately one-third of patients. The diagnosis is made by echocardiography or MR imaging.

Treatment of Thromboembolism in Cancer Patients

Objective of Treatment [43]

1. To prevent extension of the thrombus, pulmonary embolization and early recurrence of the disease

2. To prevent delayed recurrences and sequelae (e.g., postphlebitis syndrome, pulmonary hypertension)

Treatment of Venous Thromboembolism

Once venous thromboembolism has been diagnosed, the initial treatment is standard unfractionated heparin, which is generally given by continuous infusion or intermittent subcutaneous dosing [44] and followed by the administration of oral anticoagulants. These days, unfractionated heparin can be replaced by low - molecular weight heparin.[45]Cases of extensive venous thrombosis, the patients should be treated by thrombolytic agents. In case of patients with relative contraindications to system anticoagulants (such as cerebral or pericardial

metastases, primary brain tumor, or thrombocytopenia) or with absolute contraindications to system anticoagulants (such as active bleeding), the insertion of a filter (Greenfield filter) into the inferior vena cava is recommended.

1. Unfractionated heparin (UFH)

Unfractionated heparin should be given parentally by an intravenous bolus dose followed by continuous infusion. The dose of UFH is 5,000 U for the intravenous bolus and for infusion at least 30,000 U per day. Lower doses result in higher rates of recurrence.[46] The activated partial thromboplastin time (APTT) should be monitored. Keeping the APTT value at 1.5-2.5 times the control value is recommended as the target therapeutic range.[47]

2. Low-Molecular-Weight Heparins (LMWHs)

Low-Molecular-Weight Heparins (LMWHs) are fractions of UFH. LMWHs have many properties different from UFH and also have advantages over UFH.The differences[5,48-51] are:

2.1 Improved pharmacokinetic properties: LMWHs have a longer half-life and can be used in outpatient settings by subcutaneous injection without laboratory monitoring. These properties are due to their reduced nonspecific binding to heparin - binding proteins, and to their reduced binding to macrophages. LMWHs cause less bleeding with an equivalent antithrombotic effect.

2.2 Lower risk of heparin-induced thrombocytopenia

2.3 Potential lower risk of osteopenia with long-term use

3. Oral Anticoagulants

Oral anticoagulants, coumarins, are vitamin K antagonists. The most commonly used coumarin is warfarin.[26] Warfarin doses are adjusted to the prothrombin time, expressed as the international normalized ratio (INR). Warfarin should be started within 24 hours after the administration of heparin. The target INR is 2.0-3.0. Bleeding complication is associated with higher doses of warfarin. Since many drugs, especially antibiotics, interact with warfarin and cause an altered INR response, clinicians should increase the frequency of INR monitoring when initiating, discontinuing, or altering the dose of other drugs in patients receiving warfarin.[52]

4. Thrombolytic Agents

Thrombolytic agents, such as streptokinase, urokinase, and tissue plasminogen activator, are recommended only in cancer patients with a good prognosis and either a massive pulmonary embolism with hemodynamic compromise or a symptomatic ileofemoral venous thrombosis of a less than 1 week duration.[44] Absolute contraindications of using thrombolytic drugs are postoperative patients, patients with pericardial or cerebral metastases or primary brain tumors, patients with active or recent gastrointestinal bleeding including esophagitis, and patients with underlying bleeding diathesis including DIC and thrombocytopenia.[53] The regimen of thrombolytic therapy for venous thrombosis is intravenous streptokinase, given in a 250,000 U bolus dose and followed by the infusion of 100,000 U per hour for up to 72 hours. For pulmonary embolism, the dose of tissue plasminogen activator is 100 mg. given intravenously over 2 hours.[54]

5. Inferior Vena Cava Filters

Inferior vena cava filters are used to prevent pulmonary embolization of a thrombus distal to the inferior vena cava.[55] Indications for using inferior vena

cava filters are: 1) patients with venous thromboembolism who have recurrent pulmonary embolism despite adequate anticoagulant therapy 2) patients with contraindication of anticoagulant therapy which are a high potential for complications 3) patients who have recently had an adverse effect such as heparin-induced thrombocytopenia or anticoagulant- induced bleeding.

Conclusions

The hypercoagulable state is a common paraneoplastic syndrome. Tumors predispose patients to the hypercoagulable state and increase the risk of developing venous thromboembolism by several mechanisms, such as blood flow abnormalities due to comorbid diseases, blood composition abnormalities due to tumor cell procoagulants, normal host response to the tumor, hepatic dysfunction effected by tumor, and blood vessel wall abnormalities. Anticancer drugs also effect host tissue and blood vessels, and increase the risk of thromboembolism . In principle, treatment of venous thromboembolism in cancer patients is similar to the treatment in non-cancer patients. The initial treatment is administration of heparin, unfractionated heparin or low-molecular-weight heparin, followed by oral anticoagulant. Thrombolytic agents are used in extensive thrombois conditions. In case of patients with contraindications to antithrombotic agents, the insertion of an inferior vena cava filter is recommended.

Acknowledgements

I would like to express my profound gratitude to Assoc. Prof.Navapun Charurak for advice and support,and to Ms.Petra Hirsch for editing the manuscript.

References

1. Bick RL. Alterations of hemostasis associated with malignancy: etiology pathophysiology, diagnosis and management. Semin Thromb Hemost 1978 Summer; 5(1): 1 - 26
2. Goodnight SH Jr. Bleeding and intravascular clotting in malignancy. A review. Ann NY Acad Sci 1974; 230:271 - 88
3. Nand S, Fisher SG, Salgia R, Fisher RI. Hemostatic abnormalities in untreated cancer. Incidence and correlation with thrombotic and hemorrhagic complications. J Clin Oncol 1987 Dec; 5(12): 1998 - 2003
4. Falanga A, Barbui T, Rickles FR, Levine MN. Guidelines for clotting studies in cancer patients. Thromb Haemost 1993 Sep 1; 70(3): 343 - 50
5. Trousseau A. Phlegmasia alba dolens. Clinique Medicale de l'Hotel-Dieu de Paris. London: New Sydenham Society, 1865: 282 - 332
6. Billroth T. Lectures on Surgical Pathology and Therapeutics (transl from 8th ed.). New Sydenham Society, 1878.
7. Sproul EE. Carcinoma and venous thrombosis: Frequency of association of carcinoma in the body or tail of the pancreas with multiple venous thrombosis. Am J Cancer 1938 Dec; 34: 566 - 85
8. Wright IS: The pathogenesis and treatment of thrombosis.Circulation 1952 Feb; 5(2): 161-88
9. Steven SM: Diagnosis and treatment of cancer-related thrombosis. Semin Thromb Hemost 1992; 18(4): 373 - 9
10. Fibach E, Treves A, Korenberg A, Rachmilewitz EA. In vitro generation of procoagulant activity

by leukemic promyelocytes in response to cytotoxic drugs. Am J Hematol 1985 Nov; 20 (3): 257 - 65

11. Rickles FR, Edwards RL. Activation of blood coagulation in ancer.Trousseau's syndorme revisited. Blood 1983 Jul; 62(1): 14 - 31
12. Monreal M, Fernandez-Llamazares J, Perandreu J, Urrutia A, Sahuquillo J.C, Cantel E. Occult cancer in patients with venous thromboembolism: which patients, which cancers. Thromb Haemost 1997 Nov; 78(5): 1316 - 8
13. Aderka D, Brown A, Zlikovski A, Pinkhas J. Idiopathic deep vein thrombosis in an apparently healthy patient as a premonitory sign of occult cancer. Cancer 1986 May 1; 57 (9): 1846 - 9
14. Prandoni P, Lensing AWA, Buller HR, Cogo A, Prins MH, Cattelan AM, Cuppini S, Noventa F, ten Cate JW. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. N Engl J Med 1992 Oct 15; 327(16): 1128 - 33
15. Green KB, Silverstein RL. Hypercoagulability in cancer. Hematologic complication of cancer. Hematol Oncol Clin North Am 1996 Apr; 10(2): 499 - 530
16. Salzman Ew ,Hirsh J. Prevention of venous thromboembolism. Hemostasis and Thrombosis. In: Colman RW, Hirsh J, Marder J, Salzman EW, eds Basic Principles and Clinical Practice Philadelphia: J.B. Lippincott 1987. 1252 - 65
17. Falanga A, Ofosu FA, Cortelazzo S, Delaini F, Consonni R, Caccia R, Longatti S, Maran D, Rodeghiero F, Pogliani E, Marassi A, D'Angelo A, Barbui T. Preliminary study to identify cancer patients at high risk of venous thrombosis following major surgery. Br J Haematol 1993 Dec; 85(4): 745 - 50
18. Shattil SJ. Diagnosis and treatment of recurrent venous thromboembolism. Med Clin North Am 1984 May; 68(3): 577 - 600
19. Edwards RL, Silver J, Rickles FR. Human tumor procoagulants: Registry of the Subcommittee on Haemostasis and Malignancy of the Scientific and Standardization Committee, International Society on Thrombosis and Haemostasis. Thromb Haemost 1993 Feb 1; 69(2): 205 - 13
20. Gordon SG. Cancer cell procoagulants and their implications. Hematol Oncol Clin North Am 1992 Dec; 6(6): 1359 - 74
21. Nand S, Messmore H. Hemostasis in Malignancy. Am J Hematol 1990 Sep; 35(1): 45-55
22. Kies MS, Kwaan HC. Thromboembolism in cancer patients. In: Kwaan MC, Bowie EJW, eds. Thrombosis. "Philadelphia: WB Saunders., 1982: 176 - 7
23. Davis RB, Theologides A, Kennedy BJ. Comparative studies of blood coagulation and platelet aggregations in patients with cancer and non-malignant diseases. Ann Intern Med 1969 Jul; 71(1): 67 - 81
24. Sweeney JD, Killion KM, Pruet CF, Spaaaulding MB. Von Willebrand factor in head and neck cancer. Cancer 1990 Dec 1; 66(11): 2387-9
25. Uchiyama T, Matsumoto M, Kobayacshi N. Studies on the pathogenenesis of coagulopathy in patients with arterial thromboembolism and malignancy. Thromb Res 1990 Sep 15; 59(6); 955 - 65
26. Jaffe EA. Biochemistry, immunology, and cell

biology of endothelium. In: Colman RW, Hirsh J, Marder VJ, Salzman EW ,eds: Hemostasis and Thrombosis. Basic Principles and Clinical Practice, 3rd ed, Philadelphia, JB Lippincott, 1994.

27. Edwards RL, Rickles FR. The role of leukocytes in the activation of blood coagulatio Semin Hematol 1992 Jul; 29(3): 202 - 12
28. Falanga A, Ofosu FA, Delaini F, Oldani E, Dewar L, Lui L, Barbui T. The hypercoagulable state in cancer patients: evidence for impaired thrombin inhibitors. Blood Coagul Fibrinolysis 1994 Jan; 5(Suppl 1): S19 - 23
29. Rodeghiero F, Mannucci PM, Vigano S, Barbui T, Gugliotta L, Cortellaro M, Dini E. Liver dysfunction rather than intravascular coagulation is the main cause of low protein C and AT-III in acute leukemia.Blood 1934 Apr; 63(4): 965 - 9
30. Stenflo J: A new vitamin K-dependent protein: purification from bovine plasma and preliminary characteristics. J Biol Chem 1976 Jan 25; 251(2): 355 - 63
31. Esmon CT. The regulation of natural anticoagulant pathways. Science 1987 Mar 13; 235(4794): 1348 - 52
32. Liotta LA. Tumor invasion and metastasis role of extracellular matrix- Rhoads memorial lecture. Cancer Res 1986 Jan; 46(1): 1 - 7
33. Kramer RH, Vogel KG, Nicolson GL : Solubilization and degradation of subendothelial matrix glycoproteins and proteoglycans by metastatic tumor cells. J Biol Chem 1982 Mar 10; 257(5): 2678 - 86
34. Ossowki L. Plasminogen activator dependent pathways in the dissemination of human tumor cells in the chick embryo. Cell 1988 Feb 12; 52(3): 321 - 8
35. Booth BW, Weiss RB. Venous thrombosis during adjuvant chemotherapy. N Engl J Med 1981 Jul 16; 305(3):170
36. Goodnough LT, Saito H, Manni A, Jones PK, Pearson OH. Increased incidence of thromboembolism in stage IV breast cancer patients treated with a five-drug chemotherapy regimen. A study of 159 patients. Cancer 1984 Oct 1; 54(7): 1264 - 8
37. Wall JG, Weiss RG, Norton L, Perloff M, Rice MA, Korzun AH, Wood C. Arterial thrombosis associated with adjuvant chemotherapy for breast carcinoma: a Cancer and Leukemia Group G Study . Am J Med 1989 Nov; 87(5): 501 - 4
38. Saphner T, Tormey DC, Gray R. Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. J Clin Oncol 1991 Feb; 9(2): 286 - 94
39. Falanga A, Levine M.N, Consonni R, Gritti G, Delaini F, Oldani E, Julian J.A , Barbui T. The effect of very-low-dose warfarin on markers of hypercoagulation in metastatic brease cancer: Results from a randomized trial. Thromb Haemost 1998 Jan; 79(1): 23 - 7
40. Sack GH Jr, Levin J, Bell WR. Trousseua's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and threapeutic features. Medicine [Baltimore] 1977 Jan; 56(1):1 - 37
41. Rosenthal M. Niemetz J, Wisch N.Hemorrhage and thromboses associated with neoplastic

disorders. J Chron Dis 1963 Jul; 16(7): 667-75

42. Min KW, Gyurkey F, Sato C. Mucin producing adenocarcinomas and nonbacterial thrombotic endocarditis. Pathogenetic role of tumor mucin. Cancer 1980 May 1; 45(9): 2374

43. Turkstra F, Koopman MM, Buller HR. The treatment of deep vein thrombosis and pulmonary embolism. Thromb Haemost 1997 Jul; 78(1): 489-96

44. Levine M, Hirsh J: The diagnosis and treatment of thrombosis in the cancer patient. Semin Oncol 1990 Apr; 17(2): 160 - 71

45. Kuijer PMM, Gallus AS, Cade JF, Buller HR. A randomised comparison of LMWH versus standard heparin in the initial treatment of pulmonary embolism. Thromb Haemost 1995 Jun; 73(6): 974

46. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing normogram compared with a " standard care "normogram: a randomized controlled trial. Ann Intern Med 1993 Nov 1; 119(9): 874 - 81

47. Basu D, Gallus A, Hirsh J, Cade J. A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. N Engl J Med 1972 Aug 17; 287 (7): 324 - 7

48. Hirsh J, Levine MN. Low molecular weight heparin. Blood 1992 Jan 1; 79(1): 1 - 17

49. Young E, Cosmi B, Weitz J, Hirsh J. Comparison of the nonspecific binding of unfractionated heparin and low molecular weight heparin (Enoxaparin) to plasma protein. Thromb Haemost 1993 Oct 18; 70(4):625 - 30

50. Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent MK, Kelton JG. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995 May 18; 332 (20): 1330 - 5

51. Murray WJ, Lindo VS, Kakkar VV, Melissari E. Long-term administration of heparin and heparin fractions and osteoporosis in experimental animals. Blood Coag Fibrin 1995 Apr; 6(2): 113-8

52. Wells PS, Holbrook AM, Crowther NR, Hirsh J. Interactions of warfarin with drugs and food. Ann Intern Med 1994 Nov 1; 121(9): 676-83

53. Gray WJ, Bell WR. Fibrinolytic agents in the treatment of thrombotic disorders. Semin Oncol 1990 Apr; 16(2): 228 - 37

54. Markel A, ManZo RA, Strandness DE Jr. The potential role of thrombolytic therapy in venous thrombosis. Arch Intern Med 1992 Jun; 152(6): 1265 - 7

55. Becker DM, Philbrick JT, Selby JB. Inferior vena cava filters. Indications, safety, effectiveness. Arch Intern Med 1992 Oct; 152(10): 1985 - 94