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Coagulation and Cancer: Implications for Diagnosis and Management

MF LORETO, Massimo DE MARTINIS, MP CORSI, M MODESTI, L GINALDI

Department of Internal Medicine and Public Health, University of L'Aquila, Italy

Coagulation disorders are a common problem in neoplastic patients and many factors contribute to increase the risk of thromboembolic events in these patients. An hypercoagulable state is induced by malignant cells interacting directly with hemostatic system and activating the coagulation cascade. More sensitive tests to assess an hypercoagulable state in cancer patients have been developed; even though these tests are always altered in cancer patients, none of them possess a clinical significance in terms of predictive value for the occurence of thromboembolism and disease prognosis in the individual patient. The most frequent thromboembolic complications in cancer patients are deep vein thrombosis of the lower extremities and pulmonary embolism; therefore, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura or haemolytic uremic syndrome are special manifestations of neoplastic disease. Diagnosis of idiopathic deep vein thrombosis, in the absence of other risk factors, could indicate the presence of occult malignant disease; however, the need for an extensive work-up to detect malignancy is still controversial. Neoplastic patients showing a thromboembolic event should be treated with unfractioned heparin or, alternatively, with low molecular weight heparins. In order to prevent recurrence, the administration of heparin should be associated and followed by an oral anticoagulant drug. In recent years new approaches in anti-aggregation therapy have been studied, such as COX-inhibitors, cicaprost and ReoPro; further studies are needed to determine the usefulness of these molecules in treatment of malignancies. (Pathology Oncology Research Vol 6, No 4, 301–312, 2000)

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Introduction

Cancer patients show an increased susceptibility, as compared with the general population, to develop thromboembolic diseases, suggesting that disorders of coagulation are very common in this disease, although clinical symptoms occur less frequently.

The association between hypercoagulability and malignancy has been recognized, for the first time, in 1865, by professor Trousseau, who drew attention to the high incidence of deep vein thrombosis of the extremities in patients with gastric carcinoma.[109] Subsequently, several clinical and pathologic observations confirmed the increased risk of thrombosis in patients with cancer, underlying the presence of an interaction between tumoral cells and coagulation and/or fibrinolytic systems.

It is now recognized that thromboembolism is one of the most common causes of death in cancer patients. Mucin-producing carcinoma of gastrointestinal tract, ovarian, pancreatic, prostate and lung cancer,[7,90] acute promyelocytic leukemia[36] and, finally, all myeloproliferative disorders[92] are among the malignancies more frequently associated with thromboembolic episodes. A case of internal jugular vein thrombosis associated with metastatic papillary carcinoma of the thyroid has been reported,[86] and an hypercoagulable state has been described in patients with melanoma.[8] The literature reports a case of internal carotid occlusion associated with malignant peritoneal mesothelioma.[110]

Co-morbid variables may be present that would enhance the risk of thrombosis in some populations of patient with cancer, including advanced age, hypertension and heart failure, diabetes and hyperlipidemia, smoking and oral contraceptives use, immobility and, especially, surgery with an incidence up of 15%,[103] and the use of central vein catheters.[64]

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Correspondence: Dr. Massimo DE MARTINIS, Department of Internal Medicine and Public Health, University of L'Aquila, Via San Sisto 22/E, 67100 L'Aquila, Italy; *Tel:* +39 0861 429546, *Fax:* +39 0862 432858; *E-mail:* demartinis@sscaq1.cc.univaq.it

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Also chemotherapeutic agents, haematopoietic growth factors and hormonal therapy may contribute to this increased risk. Indeed, antineoplastic therapy has been reported to be correlated with coagulopathies, venous (deep vein thrombosis and pulmonary embolism) and arterial (acute myocardial infarction, angina and peripheral artery thrombosis) thrombosis and cerebrovascular events,[35] in addition to less common conditions, such as superficial thrombophlebitis of the long saphenous vein.[64]

Pathophysiology

A correlation between clotting and cancer is supported by histologic studies using immunochemical or electron microscopic techniques which demonstrate the presence of fibrin within and around primary and metastatic tumors, final product of the coagulation cascade,[19] as well as platelet microthrombi associated with growing tumor cells.[24]

Multiple mechanisms, direct and indirect, are implicated in the pathophysiology of coagulation disorders which occur in the neoplastic patient. Malignant cells directly, themselves produce various procoagulant activities (PCAs), among which, the best defined are the tissue factor (TF) and the cancer procoagulant (CP). TF is a transmembrane glycoprotein that forms a micromolecular complex with factor VII, activating the extrinsic pathway of blood coagulation. TF has been found in promyelocytic leukemia[40] and solid tumors, such as gastric and colorectal cancer[90] and it seems to be also involved in several stages of metastatic development, especially in the neovascularization process which supports hematogenous tumor dissemination.[31]

CP is a cysteine proteinase that directly activates factor X, independently from factor VII; it is found principally in malignant tissues, but also in human fetal tissue.[23] Other PCAs have been demonstrated in human tumors, including a factor XIII-like activity capable of fibrin covalent cross-linking and a factor V receptor associated with tumor cell plasma membrane that facilitates the assembly of the prothrombinase complex.[112] The potentially active subunit A of clotting factor XIII has been detected in different cell lines such as megakaryocyte, platelet and monocyte/macrophage, and it is also present occasionally in certain malignant cells. Thus, besides clot retraction, a possible role of factor XIII has been supposed in molecular interactions intracellulary and extracellulary.[1,70] It is also expressed in tumor-associated macrophages of different malignancies like giant cell tumor of bone, malignant fibrous histocytoma and several tumors of the central nervous system (glioma, glioblastoma, astrocytoma, ependymoma and meningioma).[86]

The tumor-associated macrophages, stabilizing intratumoral fibrin deposits, are implicated in tumor growth and angiogenesis, as suggested by their accumulation in fibrin deposits found in tumoral tissue samples and by the detection of coagulation factor XIIIA in and around these cells.[2]

Tumor cells also produce fibrinolytic activities; indeed, it is well-known that most tumor cells can express on their surface all proteins necessary for regulating the fibrinolytic pathways.[28] Both tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA), as well as their inhibitor, plasminogen activator inhibitor-1 (PAI-1), are expressed in various kinds of tumor cell lines and tumor tissues. u-PA expression seems to be correlated with the aggressiveness and histologic grade of some tumors, as well as clinical progression of the different carcinomas.[61] For example, u-PA can be used as predictor of prostate cancer progression; the levels of density of u-PA and its receptors are higher in patient with prostate cancer and metastasis than in healty controls and in patient with benign prostatic hyperthrophy[67] and plasma u-PA correlate to the grade of dissemination, as found by bone scintigraphy.[45] Furthermore, the measurement of u-PA in several studies may provide useful prognostic informations also in patients with colonrectal, breast and bladder cancer.[43,102,105]

Finally, among direct mechanisms, has to be considered the release of a number of different proinflammatory cytokines. The production of tumor necrosis factor (TNF-α) and interleukin-1 (IL-1β) can induce the expression of TF and PAI-1 and down-regulate the expression of thrombomodulin by endhotelial cells, resulting in reduced activation of the C protein system, one of the principal endogenous anticoagulant defence systems.[21]

In addition, tumor cells may secrete a peptide, vascular permeability factor (VPF) or vascular endothelial growth factor (VEGF) which acts as a selective mitogen and chemotactic factor for cultured endothelial cells and induces several genes in these cells, including TF,[16] playing a key role in tumor neovascularizationm.[9]

Indirectly, tumor cells contribute to the overall activation of blood coagulation by interacting with platelets, endothelial cells and monocyte-macrophages.

Intact tumor cells isolated from either human or experimental animal tumors may induce platelet adhesion or aggregation[53] by various mechanisms, such ADP production and activation[4] or activation of arachidonate methabolism.[47]

Platelets also contribute to cancer metastasis enhancing tumor cell interaction with the extracellular matrix. Among mediators involved in platelet interaction with tumor cells is 12(S)-hydroxyeicosatetraenoic acid, 12(S)-HETE, a metabolite of arachidonic acid.[49]

The platelet isoform of 12-lipoxygenase (12-LOX), enzyme metabolizing arachidonic acid to 12(S)-HETE, is expressed in a variety of human tumors. Recently several studies have shown an overexpression of 12-LOX in advanced stages of prostate cancer, that stimulates angiogenesis and tumor growth. Thus, inhibition of 12-LOX could be a novel therapeutic approach in the treatment of prostate cancer.[72]

Platelet aggregation is a recognized important mechanism for thrombus formation in many human diseases, including cancer and these platelet microthrombi may offer tumor cells some protection against the host's response, thus contributing to further disease progression.[28] Similarly, malignant cells interact with endothelial cells through membrane adhesion molecules and release of their cytokine content, inducing the adhesive potential of the endothelium and favouring the adhesion and arrest of other cells, e.g. leukocytes and platelets.

Platelet membranes contain high concentrations of integrins that are involved in platelet adhesion to the extracellular matrix. The platelet alphaIIb beta3 integrin can specifically induce platelet activation and aggregation. Honn et al. demonstrated that this integrin is not only expressed in cells of megakaryocytic lineage but also in human prostate adenocarcinoma cells and in a variety of tumor cell lines derived from different histological origin and from different species and it may participate in the metastatic progression.[15,108]

Among adhesion molecules, platelet endothelial cell adhesion molecule-1 (PECAM-1), an integral membrane glycoprotein found on human platelets and leukocytes and at the intercellular junctions of endothelial cells,[73] can regulate leukocyte trafficking through the vessel wall and it is also involved in angiogenesis.[20] Experimental evidences demonstrated that PECAM-1 gene is expressed in the genome from tumor cell lines of different species and this molecule is involved in mediating tumor cell adhesion to endothelium.[104]

Finally, malignant cells contribute to the procoagulant state inducing activation of monocytes, with subsequent expression of tissue factor.[4] Mononuclear phagocytes, like endothelial cells, do not constitutively express TF, but they expose this procoagulant on their surface in response to different stimuli including complement proteins, immune complexes and lymphokines; several studies have shown that circulating monocytes from patients with different types of cancer express increased TF activity.[90,98,99] The interaction between malignant cells and monocytes is mediated by specific adhesion receptors on the surface of both cell types and by production of inflammatory cytokines.

All these effects of malignant cells on the clotting-fibrinolytic pathways are usually associated with other factors promoting thrombosis previously mentioned, such as prolonged bed rest, vascular compression or tumor invasion and, among iatrogenic factors, chemotherapy or use of central vein catheters. Thus, cancer has been defined as the best example of "acquired thrombophilia".[28]

Hypercoagulability and Therapeutic Agents

The increased incidence of hypercoagulability during chemotherapy results from the association with other factors such as type and stage of malignancy and all the above-mentioned risk factors for thrombosis. The exact pathophysiologic mechanisms have not been completely clarified; however, several biochemical alterations involving different pathways of clotting and fibrinolysis have been reported.[35,90] Elevations in the markers of coagulation activation and reduction in the anticoagulant plasma level have been found following treatment with a variety of chemotherapeutic agents,[56] while there are few reports on the alterations of fibrinolysis and some authors have not found evidence of fibrinolysis suppression or enhancement in patients undergoing treatment.[119] Endothelial damage plays a key role in clotting activation; doxorubicin, vincristine and bleomycin cause increased platelet adhesion and endothelial retraction, resulting in exposure of the subendothelial matrix which can initiate coagulation activation.[71] Finally, chemotherapeutic agents may increase endothelial cell reactivity to platelets by inducing the release of interleukin-1 (IL-1), which facilitates adhesion molecule expression on the endothelial cell surface.[6]

Combination chemotherapy administered to patients with breast cancer may determine thrombosis. Alterations in hemostasis have been identified in breast cancer patients receiving CMF (cyclophosphamide, methotrexate and fluorouracil) and have been evaluated employing coagulative and fibrinolytic parameters such as prothrombin time (PT), antithrombin III (AT III), thrombin-antithrombin III complex, fibrinogen, tissue-type plasminogen activator (t-PA), etc.[89] In an attempt to explain these events, a recent report about CMF-chemotherapy effects on the clotting system suggests a potential interaction of these drugs with the synthesis and activation of vitamin K-dependent coagulation factors inducing abnormalities in hemostasis.[75]

Increased attention has been given to the risk of venous thromboembolism following hormonal therapy, most notably the use of tamoxifen in breast cancer adjuvant treatment. Until recently this risk was reported only in combination with chemotherapy; but in 1998 the National Surgical Adjuvant Breast and Bowel Project (NSABP) demonstrated a definitive risk independent of the presence of cancer and chemotherapeutic drugs.[29] The most widely accepted pathogenetic mechanism of thrombosis is a paradoxical estrogenic property of tamoxifen, as estrogens are known to decrease levels of antithrombin and protein C, and precipitate a thrombophilic state.

Hematopoietic colony-stimulating factors have also been reported to significantly enhance the occurrence of venous and arterial thrombosis. Several studies suggest that granulocyte-macrophage colony-stimulating factor (GM-CSF) is associated with an increased risk of vascular complications, due to an unknown thrombotic mechanism, in patients receiving either conventional or myeloblative chemotherapy, especially in those with gastrointestinal, lung, breast cancer and lymphoma.[56] Recently a phase

Ib/II trial has been conducted to determine the effect of a combination of interleukin-2 (IL-2) and GM-CSF for sixteen patients with renal cell carcinoma and pulmonary metastases. In this study no significant antitumor activity of these therapeutic agents was detected and one patient died from multifocal cerebral venous thrombosis, as revealed by autopsy.[50]

Laboratory Findings

About half of all cancer patients and about 90% of those with metastases shows alterations of one or more "routine" laboratory blood tests; the most common abnormalities described are: increases in clotting factors V, VIII, IX and XI, fibrinogen, fibrinogen degradation products and platelet count.

More sensitive tests have been developed to assess the level of activation of both the coagulation and fibrinolytic systems and have been applied in studies of cancer patient. Several of these markers have been found to be increased in patients with malignancy and they characterise the so-called "hypercoagulable state". Among these are: fibrinopeptide A (FPA), a peptide released after cleavage of fibrinogen by thrombin, a marker of thrombin activity and fibrin formation; prothrombin fragment 1+2 (F1+2), released after the activation of prothrombin to thrombin, reflecting the thrombin generation; thrombin-antithrombin III (TAT) complex, displaying thrombin generation and inhibition and, finally, D-dimer (DD), the cross-linked fibrin degradation fragments, molecular marker of fibrinolysis.[39] They can be measured by commercially available radioimmunoassays and immunoenzymatic assays.

Several studies have shown alterations in the plasma level of these markers; for example, the results of a recent study carried out in elderly, pregnancy, diabetic patients and in hematologic malignancies. These conditions display a significant increase both of the parameters indicating clotting activation (F1+2, TAT complex, FPA), and the markers of fibrinolysis (plasmin-alpha 2 antiplasmin complex and D-dimer).[62]

In another report, antithrombin III (ATIII), D-dimer (DD), fibrinogen (F) in association to prothrombin time (PT), partial thromboplastin time (PTT) and platelet count, have been recorded in 286 patients with a new primary lung cancer, in order to evaluate the potential prognostic implications of coagulation disorders in this malignancy. The authors have shown that lower values of PT, in addition to higher values of F and DD were significantly predictive of an adverse outcome.[10] D-dimer and fibrinogen levels were found significantly correlated also with the FIGO stage in a study on patients with ovarian malignancy.[113]

Furthermore, other authors investigated the activation of coagulation and fibrinolytic systems in patients with breast cancer, respectively by thrombin-antithrombin III (TAT) and antiplasmin-plasmin complex (APP) plasma levels, compared to CA 15.3 as marker of disease progression.

Elevated TAT and APP titers were found in patients with active breast cancer, compared to patients in remission and healthy controls, with a significant association with CA 15.3 level, especially with regard to TAT. This suggests an increased ability of the tumor to hyperactivate the clotting system and fibrinolysis in active breast cancer.

It is well known that the tumor cells express procoagulant activities (PCA), as tissue factor and cancer procoagulant; TF and CP can be characterised in tissue extracts by different techniques. Some reports have shown changes also in plasma levels of inhibitors of coagulation, such as reduction of antithrombin III, protein C and S, or elevation of plasminogen activator inhibitor-1 (PAI-1).[91] Furthermore, cancer patients with thrombotic events show higher level of anticardiolipin antibodies (ACLA) IgM, while an higher percentage of neoplastic patients, with and without thrombosis, have IgM and IgG ACLA level above normal limits compared with healty controls.[79]

Even though a number of tests to assess an hypercoagulable state have been developed and these tests are always altered in cancer patients, none of them is specific for cancer, nor do they possess a clinical significance in terms of their predictive value for the occurrence of thromboembolism and disease prognosis in one individual patients.[39] Thus, the identification of tests for predicting the occurrence of thromboembolic events would be of great interest, especially for those patients in need of surgery and chemotherapy, who are exposed to an increased risk.

Clinical Manifestations

The most commonly encountered thromboembolic complications in cancer patients are, certainly, deep vein thrombosis (DVT) of the lower extremities and pulmonary embolism (PE). These conditions require the same diagnostic approaches as in patients without cancer. Conversely, several unusual thrombotic complications have been observed in certain neoplasms, including migratory superficial thrombophlebitis, the Budd-Chiari syndrome, portal vein thrombosis, digital and cerebral microvascular arterial thrombosis and non bacterial thrombotic endocarditis. Recently, some cases of thrombosis of the internal jugular vein have been reported.[87,88]

The migratory superficial thrombophlebitis, the "Trousseau Syndrome", is characterised by recurrent thrombophlebitis which involve multiple superficial and unusual sites (e.g. arms, chest, etc.) with a migratory pattern and a tendency to recur. It is most frequently associated with gastrointestinal malignancies, particularly pancreatic carcinoma, and may spontaneously recover within a few days.

Hepatic vein thrombosis, the "Budd-Chiari syndrome", is notably associated with myeloproliferative disorders. It

may develop acutely or insidiously with ascites, hepatomegaly and abdominal pain, with symptoms constantly present, in addition to distention of superficial abdominal veins and splenomegaly. Sonography, computer tomography scanning, and MR imaging are useful diagnostic tools for this disease: venography by catheterization of the inferior vena cava and hepatic vein is the definitive diagnostic procedure.

Portal vein thrombosis is also associated with myeloproliferative disorders and with specific malignancies, including hepatomas, renal cell and adrenal carcinomas. It is characterised by portal hypertension leading to splenomegaly. Esophagogastric varices with subsequent bleeding may be the first symptom of this disease; and ascites is present only in acute cases.[31]

Microvascular arterial thrombosis of the extremities and central nervous system are characteristic complications of myeloproliferative diseases, in particular essential thrombocythemia and polycythemia vera. Digital ischemia may present initially as an excruciating pain in the feet, in the absence of physical signs; progression of arterial occlusion leads to pregangrenous and eventually gangrenous changes in the digits (digital ischemia has also been reported as a paraneoplastic manifestation of several types of cancer). Dizziness, vertigo and headache are neurological manifestations of polycythemia vera resulting from the alterations in the microcirculation due to hyperviscosity, while essential thrombocytemia can present with other nonspecific or focal neurologic manifestations caused by platelet occlusion of the cerebral microcirculation.[31]

Finally, non-bacterial thrombotic endocarditis has been associated with a variety of malignancies, particularly mucin-producing adenocarcinomas.[66] It is characterised by aseptic endoluminal cardiac vegetations which frequently occur on damaged valves. Their clinical manifestations are related to systemic embolization, including stroke and myocardial infarction.

If all the conditions above mentioned occur in apparently healthy patients, a careful search for underlying malignancy is required.[31]

Another complication associated with cancer is deep vein thrombosis of the upper limbs; the diagnosis of this condition may be more difficult in patients with malignancy than in those without cancer, because there are many situations producing arm swelling in the oncology patient, such as surgery (i.e. postmastectomy), tumor infiltration and extrinsic compression of the axillary or subclavian vein. More recently, the frequent use of central venous catheters in cancer patients for chemotherapy administration, transfusions and parenteral nutrition have increased the incidence of deep vein thrombosis of the upper extremities.

In a recent study of 343 patients with DVT investigated for the possible presence of occult or undiagnosed cancer (see below), the authors show that venous thromboembolism of upper limbs is more frequently associated with occult malignancy as compared with lower limbs.[34]

Special Presentations of the Thrombophilic State

Interacting with the coagulation and fibrinolytic pathways, various malignancies may also trigger several variants of disseminated intravascular coagulation (DIC).

This is a complex pathologic syndrome which complicates many well-known disorders, such as infections associated with sepsis, trauma, obstetrical complications and, obviously, neoplasia. DIC is characterised by excessive thrombin and plasmin formation,[17] with their abnormal increase within the circulation; these events cause the consumption of platelets, coagulation factors and inhibitors, and secondary hyperfibrinolysis, resulting in diffuse microthrombosis and massive bleeding.

The mechanism initiating DIC in cancer is based on the expression of abnormal tissue factor on the circulating tumor cells or on vessel surface.[12,17] A potential role of cytokines in diffuse DIC has also been supported, as the influences of inflammation and cytokines on the clotting system have become increasingly recognized.[27]

DIC is associated with all hematological malignancies, particularly acute promyelocytic leukaemia (APL), with incidence up to 100%, but it may also accompany various solid tumors, such as pancreatic, gastrointestinal and prostate cancer. Some reports have described clinical cases of prostate cancer[77] and breast adenocarcinoma,[63] both metastatic, presenting with DIC as first clinical manifestation of the tumor; in these cases the prognosis is very poor.

Clinically, the oncology patient shows more commonly a chronic and subclinical compensated form of DIC. This is usually associated with normal or slightly altered blood coagulation parameters, i.e. slight PT and PTT prolongation, hyperfibrinogenemia and increased level of fibrinogen degradation products (FDP) and platelet count. Conversely, the acute form may exhibit drastic laboratory abnormalities, sometimes even opposite to those of the chronic state, such as decreased titers of fibrinogen and others coagulation factors, decrease of antithrombin III level and platelet count, obviously in association with a dramatic prolongation of PT and PTT, and a remarkable increase of FDP.[78]

Of great interest are the results from a recently published study on the evaluation of various molecular hemostatic markers in patients with DIC before its onset and in non-DIC patients, in order to detect the possible usefulness of these markers for the diagnosis of pre-DIC. In the light of their results, an increased level of the thrombin-antithrombin complex, soluble fibrin monomer and D-dimer should be considered useful parameters in the diagnostic approach to a patient with DIC.[114]

Finally, in oncology patients, both untreated and treated with chemotherapeutic agents, particularly mitomycin C, a rare, but clinically notable complication, consists in the thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome.[38] This latter condition, characterised by renal failure, severe micro-angiopathic hemolysis and thrombocytopenia, in association with neurologic and pulmonary manifestations, has been observed more frequently in gastric, breast, colon and small cell lung carcinomas. Although its origin is unknown, recent studies suggest that the release into the plasma of an altered von Willebrand factor causes the deposition of microthrombi. This event is regulated by the production of an unknown plasma factor, resulting from alterations and apoptosis of endothelial cells.[25]

Of great interest are the results of a study on the potential involvement of nitric oxide production in TTP. The authors found increased nitrate titers in the plasma of patients developing this disease following treatment with different chemotherapeutic agents, compared to patients with de novo TTP; this can be interpreted as a result of extensive endothelial damage and subsequent release of nitric oxide.[80]

Recently a case of TTP developing during interferon alpha (IFN-alpha) therapy for chronic myelogenous leukaemia has been reported. Even though the relationship between this disease and such therapy has not been established, in this case IFN-alpha seems to be the only etiological agent.[54]

Venous Thromboembolism as First Manifestation of Cancer

In some circumstances the thromboembolic event occurs before the diagnosis of malignancy. The reported incidence of a subsequent diagnosis of cancer in patients with DVT varies from 2-25%.[41] However the hypothesis that DVT may be a predictor of subsequent development of malignancy is still controversial, given the clinical implications. Thus, different opinions have been expressed concerning the opportunity of investigating for occult malignant disease in healthy patients with so-called "idiopathic" venous thromboembolism, i.e. in the absence of obvious risk factors for thrombosis.[100]

Several studies have indicated an association between venous thromboembolism and underlying neoplasms,[18,37,69,74,82] but some authors have not found such an association.[41,76] However all previous studies are based on limited material, so their results are not generally applicable.

More recently, Sorensen and co-workers conducted an extensive study on a cohort of patients with DVT and pulmonary embolism, and the occurrence of cancer in this cohort drawn from the Danish National Registry of Patient for the years 1977-1992 and from the Danish Cancer Registry, in order to evaluate the relationship between these events and subsequent diagnosis of cancer. They have found an increased risk of several types of malignancy, particularly cancer of pancreas, ovary, liver and brain, no association was found with breast, bladder, rectal cancer and malignant melanoma.

However, calculating the standardised incidence ratio (SIR) for cancer (the ratio of observed numbers of incident cancers to those expected), this was found to be 3.0 during the first six months after discharge from hospital, decreased to 2.2 at one year and 1.1 for the remaining period of follow-up, suggesting that a thromboembolic event in a patient later diagnosed as suffering from cancer may be considered the result rather than the cause of the cancer. It seems likely that most of the malignancies found during the first year were present at the time of the diagnosis of thromboembolism.[101] Consequently, the authors recommend a search for cancer in patient with signs and symptoms of cancer and to use only simple methods for detecting malignancy, because extensive screening may cause discomfort and psychological stress in the patient.

Similar results have been obtained by Baron et al. who used the Swedish Inpatient Registry and the Swedish Cancer Registry, and studied patients between 1965 and 1983. In this study venous thromboembolism was a clear marker of cancer risk, because the SIR for cancer patients within the first year after hospital discharge was 4.4, remaining high (1.3) even 10 years after the diagnosis of cancer.[3]

With regard to the opportunity of a screening for occult malignancy in patients showing a primary thrombotic event, Hettiarachi et al. have followed prospectively,, four hundred consecutive patients with DVT for six months. This study was undertaken to evaluate the incidence of a subsequent diagnosis of cancer in patients with unexplained DVT compared to patients with secondary DVT (history of one or more of the predisposing factors) and determine whether former event can be considered a potential risk indicator of malignancy.[46] The risk of diagnosing a cancer was 4.6 times higher in patients with unexplained DVT compared to patients with secondary DVT. Thus the primary DVT may be considered, in the authors' opinion, a significant risk indicator of underlying malignancy. Conversely, other characteristics regarding the patients under study such as age, gender or localization of DVT, had no significant effect on the incidence of a new malignancy. Moreover, the majority of the patients with occult cancer showed at least some clinical abnormalities (enlarged liver, rectal bleeding, abnormal liver function tests, anemia, high blood creatinine level) at the time of presentation with DVT.

In the light of the above observations, the authors suggest an ideal clinical evaluation of these patients, comprising a medical history, physical examination, a pelvic examination, routine blood tests, including the erythrocyte sedimentation

rate, complete blood count, liver and renal functions tests, urinalysis and chest X-ray (recently this also has been supported from a retrospective analysis, in the Boston area, of a wide cohort of patients presenting with DVT). An extensive screening of all patients with unexplained DVT is unjustifiable in their opinion.[46]

To conclude, the usefulness of more expensive and, especially invasive, diagnostic tests detecting occult malignancy, need to be re-evaluated because the extensive screening procedures are associated with high costs and may themselves induce some morbidity, in addition to discomfort for the cancer patient. Thus, the cost-benefit ratio of an extensive diagnostic work-up in patients showing unexplained DVT still has to be definitively demonstrated.[84,68]

Treatment of Venous Thromboembolism (VTE)

For the treatment of venous thromboembolism, cancer patients developing an acute thromboembolic disorder should receive unfractionated heparin as a bolus of 5000 units followed by a continuous infusion of approximately 30000 units for 24 h, adjusted to maintain the activated partial thromboplastin time (aPTT) at 1.5 to 2 times the control value;[60,84] oral anticoagulants are commenced within 24 h of starting heparin.[60]

Alternatively, therapeutic doses of a low molecular weight heparin (LMWH) have been employed. The introduction into clinical practice of the LMWH in the past two decades has been one of the most exciting advances in antithrombotic therapy. In recent years several randomized trials have demonstrated that LMWH is as safe (safety is defined in relation to the occurrence of hemorrhages) and effective (the efficacy is defined as the ability to prevent symptomatic extension or recurrence of venous thromboembolism) as standard unfractionated heparin for the treatment of DVT in hospitalized patients.[81] In three recent clinical trials carried out in patients with acute proximal DVT, no differences were detected in recurrent thromboembolism between the group treated with intravenous standard heparin compared to that treated with low molecular weight heparins at home.[57,106]

The main advantages associated with use of LMWH are that laboratory monitoring is not required and only once (or twice) daily subcutaneous injections are necessary. Recent studies have suggested that heparin or low molecular weight heparin administered to cancer patients may prolong their survival. In a meta-analysis published in 1997, eight of the nine studies considered exhibit a trend of total mortality in favour of LMWH,[22] these results have stimulated renewed interest in these agents as antineoplastic agents.[84]

The administration of heparin should be associated and followed by an oral anticoagulant drug,[85] in order to prevent recurrence. Warfarin is the standard long-term anticoagulant therapy for patients with venous thromboembolism. Warfarin therapy is monitored by prothrombin time (PT). The disadvantage of this therapy is the frequent and inconvenient laboratory monitoring to maintain a therapeutic range.[60] Alternatively adjusted-dose unfractionated heparin can also he employed for long-term treatment to prevent recurrent thrombosis.[51]

As regards the duration of oral anticoagulant therapy, it is a usual practice to continue treatment for three months following a first episode of DVT and PE. Clinical trials have shown that it is advisable in cancer patients to continue anticoagulant therapy beyond three months,[97] because these subjects remain at high risk for recurrent thromboembolism, resulting from immobility, procoagulants produced by cancer cells and the use of chemotherapy.

The literature contains many reports on persistent and/or recurrent thrombosis in cancer patient, despite oral anticoagulants. Retrospective studies have reported recurrences rates between 11% and 42% in patients with different types of malignancy.[14] The strategy for the treatment of recurrent venous thromboembolism during oral anticoagulation is not rigidly standardized.[85] Prandoni and coworkers start treatment with a full-dose of unfractionated HETH or LMWH, followed by a higher dose of warfarin. In patients resistant even to high doses of warfarin, subcutaneous heparin can be administered, while in patients with a very poor prognosis, warfarin should be replaced by heparin, without waiting for warfarin failure.[84]

The anticoagulant therapy described is feasible only in uncomplicated cases of cancer; whereas patients showing active bleeding or patients with a risk for serious and important bleeding, are treated with vena cava interruption, or by placement of Greenfield filter which can intercepte potential emboli from distal thrombi.[69,84]

The risk of clinically important hemorrhage with therapeutic heparin is approximately 5%, thus, it is very important, during heparin treatment, to monitor various tests of blood coagulation, particularly the activated partial thromboplastin time (aPTT), which, if prolonged, suggests an increased risk of bleeding.[59,116] The risk in patients with malignancy has been discussed in recent studies, with conflicting results. In a multivariate analysis, tumors were associated with major hemorrhages with a relative hazard ratio of 4.07;[116] on the contrary, Prandoni et al. did not find differences in patients with cancer compared to those without cancer.[83,85]

If the prognosis of cancer is good, in particular cases, including massive pulmonary embolism, extension of venous thrombosis despite extensive anticoagulation and upper extremity thrombosis in patients who have an indwelling central venous catheter, thrombolytic therapy may be considered.[85]

The thrombolytic agents act through the conversion of plasminogen to plasmin, an enzyme that causes fibrin

degradation, thus dissolving both pathological and hemostatic plugs. In pulmonary embolism, they offer the greatest benefits for resolution of cardiac dysfunction, in the case of failure with low cardiac output. However, the main risk associated with thrombolytic agents is the occurrence of hemorrhage and when these drugs are administered in the oncology patient, the risk of hemorrhage is greater than that associated with anticoagulant therapy. Thus their usefulness is strongly limited.

Prevention of Venous Thromboembolism

Increasing attention is given to the primary prevention of venous thromboembolism because of the increased occurrence of thrombosis in cancer patients during and after chemotherapy, after surgical interventions and during the placement of indwelling central venous catheters.

The overall incidence of postoperative DVT in patients with malignancy is about 2x higher than patients without malignancy, as is as the incidence of PE,[84] In order to reduce the risk of venous thromboembolism, the most commonly utilized method of pharmacological prophylaxis is low-dose heparin (LDH) in a dose of 5000 units, commencing 2 h before operation and continuing 8 to 12 h subcutaneously after operation.

Alternatively LMWH can be employed, in a dose of 5000 units dalteparin or 40 mg, enoxaparin, initiated preoperatively and continued once daily postoperatively.[52] Two studies have focused on the efficacy of LMWH in the prevention of VTE in cancer patients undergoing abdominal operation, showing a safety profile broadly similar for the LMWH and LDH.[5,26]

Finally, although the risk of VTE associated with chemotherapy is recognized, information about its incidence and the influence of a particular chemotherapy regimen on its occurence are only available for women with breast carcinoma. A recent prospective double-bind randomized study showed that during chemotherapy low-dose warfarin (1mg.) for six weeks was an effective and safe method for preventing thrombosis in patients with metastatic breast cancer.[58]

Data regarding other histological types of tumor are currently limited, and, once again, prospective studies are required to establish thrombosis rate and thromboprophylatic strategies.

Role of Anticoagulants and Inhibitors of Platelet Aggregation in Potential Treatment of Metastases

The metastatic process involves a series of distinct steps and different components of the clotting pathway may contribute to progression of cancer; thus, inhibitors of platelet aggregation and anticoagulants could contribute to treatment of patients with metastasis.[44]

Prostacyclin, one of the most potent inhibitor of platelet aggregation, have been reported by Honn et al. reducing pulmonary metastasis and eliminating hepatic metastasis in amelanotic melanoma model.[48]

Additional studies revealed that cicaprost, a metabolically stable and orally active analogue of prostacyclin, has prominent antimetastatic effects in a series of spontaneously metastasising mammary carcinomas of experimental animals (rat, mouse) and it reduce the median number of metastases from other tumor types.[93,95, 96] The mechanism of action of cicaprost is different from cytostatic drugs, because primary tumor growth in vivo or proliferation in vitro remained unchanged. Finally, cicaprost can be used in combination with cytostatic drugs (cyclophosphamide, doxorubicin or 5-FU), without interfering with inhibition of tumor growth.[94,96]

Experimental and clinical studies suggest that heparin and vitamin K antagonists are effective compounds for the prevention of metastases.[33,107] Data from randomised trials suggest that small-cell lung cancer (SCLC) consistently responds to heparin and vitamin K antagonist, but several other tumors, including non small-cell cancer (NSCLC), colon and prostate cancer, do not respond to warfarin[13,11,55,111,117] and do not produce thrombin.[118] Further studies are needed to confirm the existing data and to determine whether haparin, vitamin K antagonists or platelet aggregation inhibitors effectively prevent the formation of metastatic tumors.

New Approaches in Anti-aggregation Therapy

In recent years several studies have been conducted on the potential use of anti-aggregation drugs for the prevention and therapy several tumor types.

The development of cyclooxygenase 2 (COX-2) inhibitors, as new nonsteroidal anti-inflammatory drugs (NSAIDs), suggests a new prospective for the treatment of human cancer. Increased levels of COX-2 have been found in inflammatory states and in neoplastic cells of human colon, breast, prostate and lung cancer and in their associated premalignant lesions.[30] Evidence has been provided that COX-2 and COX-2-derived prostaglandins may play a role in development of cancer, through stimulation of tumor cell growth and neovascularization. For example, colecoxib, an COX-2 inhibitor, shows a potent antiangiogenic activity, suppressing growth of lung and colon tumors implanted into recipient mice.[65]

Finally, Abciximab (ReoPro), a monoclonal antibody fragment inhibiting platelet aggregation through blockade of glycoprotein IIb/IIIa receptor complex, seems to have an important role in this new generation of antithrombotic drugs.

Several clinical trials demonstrated usefulness of this agent in patients with coronary artery disease undergoing balloon coronary angioplasty[32] and preliminary data sug-

gest its potential use in acute ischemic stroke.[115] Abciximab may decrease thrombus formation and the combination with heparin did not add any antithrombotic effect to Abciximab alone.[42] Further research is needed to determine the safety and efficacy of Abciximab and to provide evidence about its potential use in cancer therapy.

Conclusions

Since Trusseau's observations, the association between venous tromboembolism and cancer has been frequently demonstrated. Thromboembolic events occur in patients with a variety of malignancies.

Tumor cells possess the capacity to interact with all of the compartments of the hemostatic system, activating the coagulation cascade and stimulating the prothrombotic properties of other blood cell components; the same events while inducing a hypercoagulable state, also contribute to the processes of tumor growth, neoangiogenesis and metastatic formation.

Multiple risk factors associated with malignant disease contribute to the hypercoagulable state in cancer patients, such as stasis induced by prolonged bed rest, vascular invasion by the tumor and iatrogenic complications including the use of central vein catheters and chemotherapy. The thrombophilic state induced by antineoplastic agents is well recognized, but the pathogenesis is not completely understood. The introduction of more aggressive chemotherapeutic regimens is a possible cause of the increased incidence of thrombotic complications.

Clinical manifestations vary from localized deep venous thrombosis or pulmonary embolism, more generally associated with solid tumors, to disseminated intravascular coagulation (DIC), frequent in hematologic malignancies and metastatic cancer. The complications induced by thrombotic thrombocytopenic purpura or hemolytic uremic syndrome are observed in cancer patients.

Hemostatic abnormalities are found in more than 90% of patients with malignancies and clinically expressed as venous thromboembolic events in 15% of these patients. Several tests have been developed to assess the hypercoagulable state. However their clinical significance still needs to be defined, especially in terms of their predictive value for thrombosis.

Patients showing idiopathic VTE have an increased risk of subsequent cancer, thus when a primary thromboembolic episode is diagnosed, in the absence of other risk factors, the presence of occult cancer should be suspected. However, the usefulness of an extensive work-up to detect malignancy in terms of cost to benefit ratio still has to be demonstrated.

Finally, with regards to the management of thromboembolism in cancer, these patients must be treated with anticoagulant therapy. A large number of studies have shown that either low molecular weight heparins or standard unfractionated heparin for the treatment of acute deep vein thrombosis in hospitalized patients are equally safe and effective. After an episode of thrombosis the patients should be protected by a long term course of oral anticoagulation, remaining higher the risk of recurrence for as long as the cancer is active. Therefore, during prolonged immobilization following surgery, anticoagulant therapy must be administered to patients with malignancies because of their increased risk of venous thromboembolism compared to patients free of cancer.

Recently a new generation of anthithrombotic drugs have been investigated, inducing cicaprost, COX-inhibitors and Abciximab (ReoPro), but more evidences are needed about their efficacy in the management of cancer patient.

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