Review Article

Coagulation Abnormalities in Malignancy

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INTRODUCTION

The close relationship between tumor growth and the activation of blood coagulation has been known since 1865, when Armand Trousseau described the clinical association between idiopathic venous thromboembolism (VTE) and occult malignancy.[1] In 1878, the pathologist Billroth published his observations of fibrin clots in vessels draining malignant tumors at postmortem,[2] a finding confirmed 60 years later by Sproul and colleagues[3] and expanded in a large series by Saphir and colleagues,[4] in which 35% to 50% of autopsies of cancer patients revealed significant tumor-associated thrombosis. These observations from patients with cancer were defined further by: (1) relatively specific histochemical staining for fibrin[5]; (2) immunochemical identification of fibrin[6]; (3) electron microscopic confirmation of the characteristic periodicity of fibrin in apposition to tumors[7-11]; and (4) specific uptake of radiolabeled fibrinogen in experimental tumors[10,11] and human tumors.[12]

It is now clear that cancer patients are at much higher risk for the development of VTE - a realization that has stimulated the design of randomized, controlled intervention trials in this patient population to determine the best method for prevention of this significant cause of morbidity and mortality.

PATHOGENESIS

Virchow's Triad

Patients with cancer have multiple reasons to develop VTE, which can be classified according to the same mechanisms first proposed by Rudolph Virchow in 1856[13] to explain the pathophysiology of all VTE. More recently, these mechanisms have been restated in the context of the cancer patient by Green and Silverstein[14] as follows: stasis; vascular damage; hypercoagulability. Cancer patients often suffer from stasis as a result of prolonged bed rest or obstruction of vascular flow from extrinsic compression or direct vascular invasion by tumor. Vascular damage may occur secondary to direct invasion by tumor, use of CVADs, and most commonly, administration of cancer chemo-

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therapy drugs. Indeed, virtually all of the commonly used intravenous cancer chemotherapy agents are capable of activating blood coagulation in vivo, presumably related to induction of vascular injury.[15] Finally, cancer patients have a primary hypercoagulable state the pathogenesis of which is exceedingly complex. The primary interactions between cancer cells and the vessel wall, which are thought to lead to thrombosis, are represented diagrammatically in Figure 1.[16] These mechanisms reflect an aberrant host inflammatory response to a foreign invader - the tumor cell.[14,16,17,18]

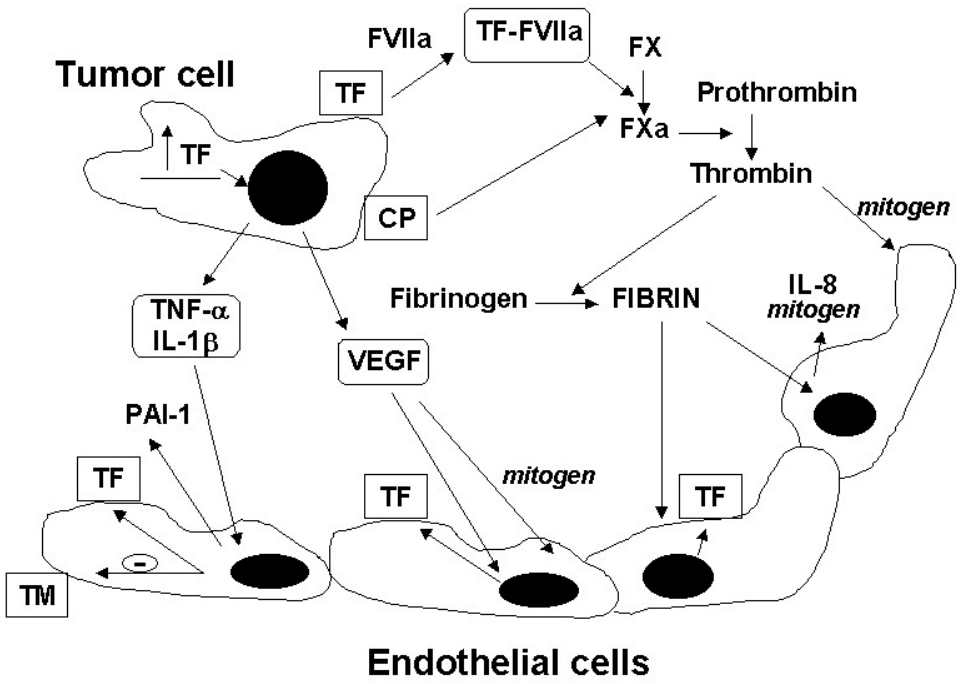

Figure 1. Regulation of tumor cell and endothelial cell procoagulant functions in the pathogenesis of thrombosis in cancer. Tissue factor (TF) and cancer procoagulant (CP) are synthesized and expressed on the surface of tumor cells. The effects of these tumor cell procoagulants are enhanced by the local production of the important proangiogenic cytokines interleukin-8 (IL-8) from the endothelial cells and vascular endothelial growth factor (VEGF) and the inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) from tumor cells. These cytokines convert the normal anticoagulant endothelium to a procoagulant endothelium as follows: (1) downregulation of thrombomodulin (TM) expression; (2) increased synthesis of TF and plasminogen activator inhibitor-1 (PAI-1). Fibrin, produced in response to activation of clotting by TF and CP, increases both TF and IL-8 production by the endothelium, further enhancing thrombogenesis and angiogenesis. TF also increases angiogenesis by the tumor cell by increasing the synthesis of VEGF.

Direct-Acting Tumor Procoagulants

Tumor cells themselves possess a variety of procoagulant properties, including the constitutive, cellular expression of the potent procoagulant tissue factor (TF), the secretion of the cysteine protease cancer procoagulant (CP), and the secretion of indirect procoagulant cytokines such as interleukins IL-1 and IL-8, tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF). The latter cytokines induce procoagulant properties in adjacent and distant host cells. For example, tumor cell VEGF is chemotactic for both macrophages and endothelial cells, activating TF in both cell types. Tumor cells also activate platelets and, via integrin expression, form adhesive interactions with platelets and the endothelium of blood vessels.

The human TF molecule molecule is a single-chain 263-amino acid, 47-kDa transmembrane glycoprotein. It acts as both a surface receptor and cofactor for activated coagulation protease factor (F) VIIa. Upon binding of FVIIa to TF, blood coagulation is initiated with downstream generation of activated coagulation serine proteases, FXa and FIIa (thrombin). TF activity is dependent upon its expression in conjunction with a suitable lipid surface that can be provided by a variety of tumor cells.[19] TF is seldom expressed in normal epithelial tissue, but is frequently expressed as a result of malignant transformation. TF expression not only correlates with the degree of histological dedifferentiation in a number of solid tumors, but it also appears to alter tumor cell phenotypic behavior.

Thrombin, ultimately generated as a result of the conversion of prothrombin by the prothrombinase complex, interacts with protease-activated receptor 1 (PAR-1) expressed on a number of epithelial-derived tumor cell lines. The binding of thrombin to its receptor has a number of cellular effects in cancer including upregulation of TF expression and enhanced procoagulant activity in colon adenocarcinoma cell lines; the enhanced expression of urokinase plasminogen activator in prostatic carcinoma and enhanced invasive potential of breast carcinoma cells. Thrombin also upregulates expression of the VEGF receptor on endothelial cells.[20]

Clearly, local peritumor activation of coagulation may have important effects in the biology of cancer and interference with this activation by antithrombotic agents may result in alterations in tumor biology.

Indirect-Acting Tumor Procoagulants - Tumor-Host Cell Interactions

Tumor cell interaction with the vessel wall reduces endothelial cell secretion of tissue plasminogen activator (tPA) and expression of thrombomodulin (TM), and increases endothelial cell synthesis of plasminogen activator inhibitor (PAI-1). Finally, substantial experimental evidence supports the presence of increased numbers of activated monocytes/macrophages in the circulation of cancer patients and in proximity to growing tumors. These antigen-pro-

cessing cells express TF on their surface, presumably as part of the host immune response to the tumor and/or in response to secretion of tumor products. Tumor-associated macrophages have been shown to assemble the entire coagulation cascade and form cross-linked fibrin on their surface in apposition to growing tumor.[17] The activation of coagulation in the tumor microenvironment, which routinely spills into the circulation of cancer patients, may be a primitive effort on the part of the host to limit the spread of tumor cells. Of interest, macrophage TF expression in cancer patients (measured in cultured peripheral blood monocytes) correlates significantly with plasma levels of fibrinopeptide A (FPA), the first cleavage product of thrombin's action on fibrinogen.[17] Although correlation never proves causation, it is notable that cross-linked fibrin can be colocalized with TF in both tumor-associated macrophages and within the endothelium of tumor-associated blood vessels in human breast and lung cancer.[21,22] The latter finding (i.e., TF expression in endothelial cells only in proximity to or within a growing tumor) lends further support to the concept that the new vessels, formed as a result of angiogenic signals generated by tumors, may be more susceptible to thrombogenesis.[22] Further, this observation has stimulated further exploration of a possible role for TF in the development of tumor angiogenesis[23,24] and as a marker of the so-called angiogenic switch,[25] the mechanism(s) by which otherwise normal endothelial cells become neoangiogenic.

HEMOSTATIC DISORDERS

Thrombocytopenia or Thrombocytosis

Quantitative platelet abnormalities are common in cancer patients, particularly in patients with solid tumors such as carcinomas of the lung and liver, as a complication of Hodgkin and non-Hodgkin lymphomas, and in chronic myeloid leukemia.[26-29] Thrombocytopenia is the principal cause of bleeding in untreated cancer patients,[30] reflecting reduced production, increased destruction, or sequestration within an enlarged spleen.[27] Reduced production in cancer is usually secondary to replacement of bone marrow by tumor cells, sepsis, vitamin B12 or folate deficiency, or ineffective thrombopoiesis, and may result from the elaboration by tumor cells of mediators that inhibit platelet production.[26,27,31-33] Modest thrombocytosis (above 400,000 to 800,000/μL) is common, occurring in up to 60% of untreated patients in some series[26,28,29,31,33-37] and may provide an early marker of occult cancer.[29]

Several studies have called attention to increased platelet turnover and to evidence of platelet activation and consumption in patients with malignancy, abnormalities that generally respond to successful treatment of the underlying neoplasm.[38-41] Patients with very short platelet survival times tend to have the worst prognose.[39] Disseminated intravascular coagulation (DIC) is probably the most common cause of increased platelet consumption, and platelet counts, whether elevated or depressed, may reflect the overall degree of compensation in

DIC. This chronic form of DIC, however, may not be overt and may not present with laboratory abnormalities (i.e., prolongation of the prothrombin time, activated partial thromboplastin time, and thrombin time) typical of acute DIC.

A symptom complex resembling idiopathic thrombocytopenic purpura (ITP), with accelerated, apparently immune, destruction of platelets has been reported repeatedly in patients with a variety of tumors, including Hodgkin disease, acute and chronic lymphocytic leukemia, and carcinomas of many sites; in these patients, thrombocytopenia may precede clinical evidence of neoplasia.[27]

Thrombocytopathy

Qualitative abnormalities of platelet function are not uncommon abnormalities in cancer patients and include reduced adhesion; impaired, increased, or spontaneous aggregation; and poor clot retraction.[42] A thrombocytopathy often accompanies dysproteinemia, in which tumor-secreted paraproteins coat platelets and interfere with their function; thrombocytopenia and/or clotting factor deficiencies also occur in these patients.[26] One or more of these defects is observed in up to 15% of patients with IgG myeloma, 38% of patients with IgA myeloma, and 60% of patients with Waldenström macroglobulinemia exhibit such abnormalities. An acquired storage pool defect and other selective biochemical defects in the platelets have been described in cancer patients.[43,44]

Disseminated Intravascular Coagulation with Consumptive Coagulopathy

Clinically overt DIC with a consumptive coagulopathy and hemorrhage occurs infrequently in patients with cancer, except occasionally as a complication of therapy and in association with the tumor lysis syndrome. However, in patients with acute promyelocytic leukemia (APL), prior to the introduction of all-trans retinoic acid (ATRA) as standard induction therapy, the incidence of this complication of the chemotherapy was as high as 50%.[45] Much more common in cancer patients are subclinical hemostatic abnormalities manifested only as the result of laboratory testing. Cooper and colleagues coined the term compensated DIC to distinguish this group of patients from those to have decompensated DIC. Nevertheless, these patients have been proven to be highly susceptible to the development of overt DIC.[46]

Abnormalities of one or more of the routine tests of coagulation have been reported in approximately 50% of all cancer patients at the time of presentation (before therapy), increasing to 90% of those patients with metastases.[33,46-48] The results of a serial study of 215 cancer patients reported by Edwards and colleagues[37] revealed the most common abnormalities at the time of entry into the study to be: (1) an elevated platelet count; (2) elevated plasma fibrinogen; and (3) elevated plasma levels of fibrinopeptide A (FPA). Although these individual findings are not specific and may be

Table 1. Laboratory evidence for activation of clotting in blood samples from cancer patients

- Elevated levels of fibrinopeptide A and prothrombin F_{1+2}
- Elevated levels of thrombin-antithrombin complexes, fibrin monomers and fibrin D-dimers
- Increased plasma levels of tissue factor, factor Vlla, and tissue factor pathway inhibitor (TFPI)
- Reduced levels of antithrombin lll, protein C, and free protein S
- Activated protein C resistance (in the absence of the factor V Leiden mutation)

part of an acute-phase response or, in the case of thrombocytosis, may occur as the result of hemorrhage or iron deficiency, nevertheless they are consistent with the definition of "compensated DIC." Blood coagulation laboratory values (in particular FPA levels) in this study became progressively more abnormal with disease progression.[37] Many other clotting abnormalities have also been reported in cancer patients (Table 1).[49]

These seemingly variable and even contradictory laboratory findings are to be anticipated in a disease in which excessive, but generally low-grade, coagulation, fibrinolysis, and compensatory homeostatic mechanisms are proceeding at different and changing rates. Individual cancer patients may lie at any point along a spectrum that extends from a "prethrombotic" or "hypercoagulable" sate to DIC of varying degrees of severity and compensation. Cancer patients exhibit widely varying levels of DIC, from milder, more chronic forms without bleeding sequelae to severe forms with catastrophic bleeding. The underlying principle in all of these patients is that the clotting system is activated systemically, clotting factors are consumed, and fibrinolysis is activated.

In some cancer patients, clotting abnormalities are detected only with more sophisticated tests. Thus, the reported incidence of hemostatic abnormalities is not only a function of the type of tumor, the extent of tumor burden, and treatment; it also may be highly dependent on the sensitivity and specificity of the laboratory tests used. None of the clotting tests currently available is specific for cancer and, with the exception of the small study published by Falanga and colleagues,[50] no pattern of abnormal clotting studies has been demonstrated capable of predicting with a reasonable degree of certainty either bleeding or thrombosis in cancer patients.[51]

THROMBOTIC DISORDERS

The Association Between VTE and Occult Cancer

Patients who present with idiopathic deep vein thrombosis (DVT) have an increased risk of subsequently developing cancer compared with patients with secondary DVT and to patients with symptoms of DVT, but who are not found to have DVT.[52] In a population-based study conducted in Sweden for patients hospitalized between 1965 and 1983, Baron et al. calculated

the standardized incidence ratios (SIRs) for cancer in patients with VTE.53 The SIR at 1 year following the diagnosis of VTE was 4.4. In a study using a similar database-linkage strategy on Danish hospital and cancer registries for the years 1977-92, Sorensen et al. found the SIR to be 1.3 for VTE.54 The SIRs were highest within the first 6 months and dropped close to 1.0 beyond 12 months of presentation with VTE. Finally, Schulman and Lindmarker used the Swedish cancer registry to determine the incidence of subsequent cancer diagnosis in patients from a trial on the duration of anticoagulant therapy.[55] The SIR for the development of cancer was approximately 4.0 in the first year after an idiopathic thromboembolic event. The cumulative probability of cancer over 6 years of follow-up in those subjects categorized as having idiopathic VTE was 17%, compared with 5% in patients with secondary VTE.

Based on the reported association between VTE and occult cancer, it has been suggested that patients presenting with idiopathic thrombosis should undergo extensive investigations for an underlying cancer. There has been much discussion concerning this issue because the potential benefit of screening for occult malignancy must be weighed against potential harms such as procedure-related morbidity, the psychological burden of a false-positive test and the cost of screening procedures. A small randomized trial evaluating extensive screening vs. no screening in patients presenting with idiopathic VTE has been conducted.[56] The battery of tests used in the extensively screened group included: ultrasound and computed tomography of the abdomen and pelvis, a fecal occult blood test, gastroscopy, colonoscopy, sputum cytology, mammography, a pelvic examination, a prostate examination, and tumor markers. Thirteen of the 99 patients in the extensively screened group had cancers detected initially compared with none of the 102 patients in the control group. However, 10 patients in the control group and one in the screened group developed cancer during the 2-year follow-up period. There was no statistically significant difference detected in cancer-related mortality in the two groups, 3.9% vs. 2%, respectively. Given such results, it is premature to recommend extensive screening in patients who present with idiopathic VTE.

PREVENTION OF THROMBOSIS IN CANCER

Surgical Prophylaxis

Cancer patients undergoing surgery are at increased risk for postoperative thrombosis compared with non-cancer patients.[57] Clinical trials have demonstrated the efficacy of subcutaneous unfractionated heparin (UFH) in preventing DVT and pulmonary embolism (PE) in patients undergoing major surgery.[58,59] In these studies, many of the patients had cancer.[58] Mismetti et al. have conducted a meta-analysis of trials that compared a low molecular weight heparin (LMWH) to UFH in high-risk major surgery.[60] In the analysis of the eight trials that included patients undergoing surgery for can-

cer, no differences in asymptomatic DVT, clinical PE, death or major bleeding were detected between LMWH and UFH. The results of these studies provide evidence that once-daily LMWH is as safe and effective as several injections of UFH per day for the prevention of postoperative DVT in cancer patients. The once-per-day injection is attractive because of the comfort for patients and convenience for medical staff. In recent years, a number of trials have shown that the incidence of venographic DVT can be reduced with extended out-of-hospital prophylaxis with LMWH in patients undergoing major joint-replacement surgery. A meta-analysis of these trials has suggested that the rate of clinical DVT after hip replacement is also reduced with the longer treatment.[61] Based on the results of these trials and the notion that the risk of VTE extends beyond the immediate postoperative period in patients undergoing cancer surgery, Bergqvist et al. studied extended prophylaxis in cancer surgery. In the Enoxacan II study, patients undergoing surgery for abdominal malignancy received one week of enoxaparin and were then randomized to enoxaparin or placebo for another 21 days.[62] Bilateral venography was performed at the end of treatment. There was a statistically significant reduction in DVT from 12% with placebo to 4.8% with extended prophylaxis.

Extended prophylaxis in cancer surgery is potentially an important advance in the care of cancer patients undergoing surgery. However, further research is required to show that continuing anticoagulant therapy beyond hospitalization will also reduce the risk of clinically important VTE.

Prophylaxis in the Medical Cancer Patient

There are far fewer data available on prophylaxis in ambulatory cancer patients. Although it was recognized that tamoxifen was thrombogenic in women with breast cancer, the results of the Breast Cancer Prevention Trial conducted by the NSABP provided an opportunity to estimate the thrombogenic effect of tamoxifen alone.63 In this trial, healthy women at risk for developing breast cancer were randomized to either tamoxifen or placebo for 5 years. There was an increased risk of DVT in the tamoxifen group compared with placebo: 0.13% per year vs. 0.084% per year. The corresponding rates for PE were 0.069% and 0.023%, respectively. In this trial, the highest rates of thrombosis associated with the use of tamoxifen were observed in women > 50 years of age. Clinicians are often faced with the scenario of a patient with a past history of VTE who develops breast cancer and requires therapy with a hormonal agent. Based on the results of a recent trial, an aromatase inhibitor that has a much lower risk of thrombosis than tamoxifen can be used.[64]

In one randomized controlled trial patients with metastatic breast cancer receiving chemotherapy were randomized to low-intensity warfarin (target INR 1.3 to 1.9), or placebo.[65] Prophylaxis with the oral anticoagulant was associated with an 85% relative reduction in the rate of thromboembolism without an increase

in bleeding. Despite these results most oncologists do not use primary prophylaxis in patients with advanced cancer on chemotherapy. A suggested approach is to consider a patient's underlying baseline risk of VTE and then weigh the absolute reduction in the risk of VTE versus the risk of anticoagulant-induced hemorrhage.

Another group of patients that has emerged to be at high risk for thrombosis are patients with brain tumors who are on extended follow-up. In a review by Marras et al. rates of symptomatic VTE as high as 18% per year were reported.[66] Weijl et al. reported that 8.4% of 179 patients with germ cell tumors who received platinum-based chemotherapy developed thromboembolism.[67] Finally, interest in the thrombogenicity of anticancer agents has been rekindled amongst medical oncologists because of the unexpectedly high rate of VTE in cancer patients receiving novel anticancer agents aimed at specific molecular targets in the cancer cell, e.g. anti-VEGF, anti-EGFR, and thalidomide.[68-73]

Central Vein Catheter Thrombosis

Thrombosis associated with central vein catheters can be particularly problematic in the cancer patient. Studies of warfarin (1 mg per day) and of LMWH (dalteparin 2,500 units daily) had demonstrated significant reductions in catheter thrombosis.[74,75] Many of the thrombotic events were asymptomatic. Despite the results of these trials, routine prophylaxis is not practiced and there is substantial variation in the use of antithrombotic regimens. Recently, the results of two randomized trials in patients with central vein catheters were reported: one compared dalteparin with placebo[76] and the other compared low-dose warfarin (1 mg) with placebo.[77] The rates of clinically relevant thrombosis were very low (4% and less) in both patient groups and no difference was detected between groups in either study. The reason for the observed low rates of thrombosis in these trials are unclear. One possible explanation is that newer generations of catheters and improved catheter care have reduced the rates of associated thrombosis.

Treatment of VTE

Treatment of cancer patients with VTE is difficult because these patients have an increased risk of recurrent VTE and also of anticoagulant-induced bleeding compared with non-cancer patients. In addition, many cancer patients have a compromised quality of life and the occurrence of thrombosis has an additional negative impact on their quality of life.

Studies have confirmed that cancer patients with acute VTE are at increased risk of recurrent VTE and anticoagulant-induced bleeding compared with non-cancer patients.[78,79] In addition, cancer patients who develop VTE have increased mortality compared with cancer patients without VTE.[80]

Risk of Recurrence and Bleeding

Hutton et al. performed a retrospective analysis of the rates of recurrent thrombosis and bleeding for patients who received at least 3

months of oral anticoagulant therapy in two large randomized clinical trials that compared LMWH with UFH for the initial therapy of acute VTE.[78] The incidence of recurrent thrombosis in patients with cancer was 27.1 per 100 patient-years vs. 9.0 per 100 patient-years in those without cancer, p = 0.003. The risk of bleeding was approximately six times higher in cancer patients (13.3 per 100 patient-years) than in patients without cancer (2.1 per 100 patient-years) (p = 0.002).

More recently, Prandoni et al. reported on the outcomes of anticoagulant treatment in a cohort of 842 patients who received initial UFH or LMWH followed by oral anticoagulants for acute VTE.[79] The 12-month cumulative incidence of recurrent thromboembolism in the 181 cancer patients was 20.7% vs. 6.8% in patients without cancer, for a hazard ratio of 3.2. The 12-month cumulative incidence of major bleeding was 12.4% in patients with cancer compared with 4.9% in patients without cancer, for a hazard ratio of 2.2. Recurrence and bleeding were both related to cancer severity and occurred predominantly during the first month of anticoagulant therapy.

Initial Treatment of VTE

Based on the results of numerous randomized controlled trials, LMWH has replaced UFH as the first-line treatment in the majority of patients with acute VTE. Large meta-analyses of these clinical trials have shown that weight-adjusted subcutaneous LMWH is safer and probably more effective than UFH administered by continuous intravenous infusion and monitored[84] by the activated partial thromboplastin time.[81-]

Despite the observed efficacy and safety of LMWH in these trials, it should be noted that only about 20% of patients in these studies had cancer. Nonetheless, it would seem reasonable to generalize the results of these trials to cancer patients with acute VTE. In terms of optimizing treatment, the use of LMWH avoids intravenous administration of anticoagulant therapy and the need for laboratory monitoring, thereby improving the quality of life of the patient.

Three clinical trials have demonstrated that patients with acute proximal DVT can be treated safely at home with subcutaneous LMWH without admission to hospital.[85-87] In these trials, some of the patients were treated entirely at home and some were admitted to hospital for a short while and then discharged home early. In these trials, approximately 400 cancer patients received either LMWH or UFH. The rate of recurrent VTE at 3 months was approximately 10% in both treatment arms. Additional cohort studies have shown that about 80% of unselected outpatients with newly diagnosed DVT can be treated entirely at home, and up to 50% of these patients had cancer.[88,89] Hence, use of LMWH at home in the cancer patient with acute VTE is recommended because of the substantial positive impact on quality of life. Clearly, some patients with acute VTE will require hospitalization because of symptoms and other complications related to their cancer. If

patients are to be treated at home, they must be reliable and compliant, and have a good support system.

In contrast to DVT, relatively few trials have compared LMWH with UFH in patients with acute PE. Simmoneau et al. compared the LMWH tinzaparin with intravenous (i.v.) UFH in hospitalized patients with PE, and no difference was detected in recurrent VTE and bleeding between treatment groups.[90] In the trial performed by the Columbus Investigators, which found no difference in these outcomes between the LMWH reviparin and UFH, the majority of patients were treated at home, and 27% of all patients had PE.[87] In these two trials, 10% and 23% of patients had cancer, respectively. Finally, in a prospective cohort study, Kovacs et al. treated 108 patients with PE as outpatients with the LMWH dalteparin; 22% had cancer.[91] The rate of recurrent thrombosis was 5.6%, and major bleeding occurred in 2.9% of the patients. Hence, based on this evidence and the large experience with LMWHs in DVT, it seems reasonable to manage acute PE patients who are hemodynamically stable by treating them with outpatient LMWH. However, in patients with acute PE who are hemodynamically unstable, the use of i.v. UFH should be considered because such patients were excluded from the clinical trials that compared LMWH with UFH. The use of IVC filters will reduce the short-term risk of PE, but is associated with an increased risk long-term of recurrent DVT, despite concurrent oral anticoagulant therapy. In a large randomized trial conducted in France, in which patients with proximal DVT were treated with anticoagulant therapy and randomized to receive an IVC filter or not, there was a statistically significant reduction in PE during the first 2 weeks of treatment.[92] By 1 year, however, there was a statistically significant increase in recurrent DVT in patients with a filter. This was probably a result of thrombosis that developed around and proximal to the filter. Thus, the use of an IVC filter in a cancer patient presenting with acute VTE is not recommended. Filters should be reserved for patients who are actively bleeding and cannot receive anticoagulant therapy, and for patients who develop multiple episodes of recurrent thromboembolism despite therapeutic LMWH.

There are recent reports on a new type of IVC filter (the Gunther Tulip retrievable vena caval filter), which could potentially be useful in a cancer patient who presents with acute VTE and is actively bleeding.[93] In such patients, a filter can be inserted and then removed within 7-10 days if the bleeding has stopped and is well-controlled. This would avoid the long-term potential complications of IVC filters. However, the results of additional studies on cancer patients are required.

Long-term Anticoagulant Therapy

Long-term anticoagulant therapy using coumarin derivatives is required to prevent recurrent thrombosis. An oral anticoagulant such as warfarin is commenced on the first or second day of treatment and the aim is to achieve an

international normalized ratio (INR) of between 2.0 and 3.0. Warfarin therapy is particularly complicated in the cancer patient for a number of reasons. It is often difficult to maintain the INR within the therapeutic range because cancer patients suffer from anorexia and vomiting. In addition, drug interactions (e.g. chemotherapy and antibiotics) can influence the anticoagulant effect of vitamin K-dependent anticoagulants. Often it is necessary to frequently interrupt oral anticoagulant therapy because of thrombocytopenia and procedures such as thoracentesis and abdominal paracentesis. Finally, frequent blood sampling is required for the INR and venous access can often be difficult in the cancer patient.

There are certain features of long-term anticoagulant therapy with LMWH that are attractive in the cancer patient. LMWH does not require laboratory monitoring and can be administered once or twice daily, subcutaneously based on body weight. There is the clinical impression that LMWH can be effective in warfarin resistance. Finally, based on preclinical data and meta-analyses, there is the potential for less bleeding. A number of trials have compared long-term oral anticoagulant therapy with long-term LMWH.[94-99] These trials were relatively small in size and had very few cancer patients. No definitive conclusions can be drawn from these trials concerning long-term treatment with LMWH in the cancer patient.

Several recent randomized trials, however, have provided new information concerning the long-term treatment of cancer patients with VTE. In the trial reported by Meyer et al., cancer patients with acute VTE were randomized to 3 months of enoxaparin or warfarin at a targeted INR of 2.0-3.0.[100] The primary outcome measure was a composite outcome consisting of major bleeding and recurrent VTE. In the 71 patients who received warfarin, the outcome event rate was 21% compared with 10.5% in the 67 patients who received LMWH, $p = 0.09$. This observed difference was mainly as a result of the rates of major bleeding in the two groups; 16.9% in warfarin patients vs. 7.5% in the LMWH patients. Recently, Lee et al. reported the results of the CLOT trial in which cancer patients with acute VTE and/or PE were randomized to long-term dalteparin vs. long-term oral anticoagulant therapy.[101] Over the 6-month study period, 27 of 336 patients in the dalteparin group compared with 53 of 336 patients in the oral anticoagulant group experienced recurrent VTE. The probability of VTE at 6 months was reduced from 17.4% in the oral anticoagulant group to 8.8% in the dalteparin group, hazard ratio 0.48, $p = 0.0017$. No statistically significant difference was detected in major bleeding between groups, 3.6% and 5.6%, respectively. Finally, in a subgroup analysis of a trial that compared long-term tinzaparin LMWH with oral anticoagulant therapy, both administered for 3 months, there was a statistically significant reduction in recurrent VTE in the subgroup of cancer patients.[102] Based on the results of these trials, long-term therapy with LMWH is an im-

portant advance in the management of cancer patients with acute VTE. It substantially reduces the rate of recurrent VTE without an increase in bleeding, thereby improving the quality of life of the cancer patient.

A number of novel agents that target specific coagulation proteases are currently undergoing investigation for both the prevention and treatment of VTE.[103] Such agents could potentially improve thrombosis management in cancer patients.

Antineoplastic Effect of Anticoagulants

The potential for anticoagulant therapy to reduce mortality in cancer patients as a result of an antitumor effect was briefly reviewed.[104] Recently there have been a number of meta-analyses of trials of LMWH vs. UFH for the initial treatment of acute VTE that have all demonstrated a reduction in mortality in favor of LMWH.[82,105-107] The observed reduction was due to the effect in the subgroup of cancer patients. In these trials the difference was not explained by a reduction in fatal PE. Another trial, which compared a short course of LMWH with UFH for the prevention of postoperative thromboembolism in patients with breast and pelvic malignancies, showed a significantly improved 2-year survival in the patients who received the LMWH.[108] However none of these trials were designed with survival as the primary outcome. Kakkar et al. recently reported the results of a trial that was specifically designed to test the effect of LMWH on survival in patients with cancer.[109] In the FAMOUS trial 385 patients with advanced solid tumors were randomized to the LMWH dalteparin or placebo for up to 1 year. No difference was detected in survival at 1 year. However, in a subgroup analysis of good-prognosis patients, there was a statistically significant improvement in survival in favor of the LMWH. These results are encouraging, and the first trial specifically designed to evaluate the antineoplastic effect of LMWH has been conducted and hopefully will be an impetus for further trials.

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