

Thrombotic and Bleeding Complications Associated with Chemotherapy

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Abstract

It is well recognized that cancer patients have an increased risk of thrombosis and bleeding. Contributory factors to thrombotic complications include prothrombotic risks carried by many chemotherapeutic agents, type of cancer, stage of cancer, age, and comorbidities. Surgical procedures and the presence of an indwelling vascular device, often used as a mode of delivery for chemotherapy, further increase the risk. Correlative studies have demonstrated upregulation of coagulation in response to chemotherapeutics, and clinical studies have shown that various cancer treatments are independent risk factors for thrombotic complications. It has also been shown that patients who develop thrombosis during treatment have a worse overall prognosis. Mechanisms for chemotherapy and cancer-associated thrombosis are not well understood. Better insight into the mechanism for thrombosis may help better identify those cancer patients at highest risk, who may then benefit from up-front anticoagulant prophylaxis.

Keywords

- ▶ adverse drug reactions
- ▶ bleeding
- ▶ cancer
- ▶ chemotherapy
- ▶ thrombosis

Since Trousseau first lectured on “phlebitis alba dolens” in his patients with gastric cancer,¹ the association between cancer and thrombosis has been well documented. The incidence of thrombosis in the cancer patient is 30% higher than the general population² and is higher in those with hematologic malignancies. It is notable that during chemotherapy, the incidence is even higher.³ Many contributory factors account for the increased risk for thrombosis. Among them is the use of therapeutic agents with prothrombotic properties. However, in clinical practice, these agents are almost always given in combination in various regimens designed for a given type of cancer. The thrombotic risk in a combination regimen is frequently higher than when a single drug is used. A good example is when thalidomide is used in combination with high-dose dexamethasone and anthracyclines for the treatment of multiple myeloma; the incidence of thrombosis can be as much as 10-fold higher than that with thalidomide alone.⁴ Thus, the risk of thrombosis is dependent not only on the type of cancer but also on the therapeutic regimens. In this article, some of the thrombogenic properties of individual chemotherapeutic agents are first reviewed. This is followed by discussion of the actual observed incidence of

thrombotic complications when they are used in combination chemotherapy in various malignant disorders.

Thrombogenic Properties of Common Chemotherapeutic Agents (Listed Alphabetically)

All Trans-Retinoic Acid and Arsenic Trioxide

Both of these agents are used primarily for the treatment of acute promyelocytic leukemia (APL). They cause differentiation of the promyelocytic leukemic cells, and in combination with anthracyclines, complete remission is seen in over 90% of patients. Thrombotic complications are common in APL. APL is a highly prothrombotic disorder by itself, and when thrombosis occurs during treatment with all trans-retinoic acid (ATRA), it is often difficult to distinguish this as part of the natural history of APL or as a complication of the drugs used. The APL promyelocytes produce tissue factor (TF) and the fibrinolytic inhibitor plasminogen activator inhibitor 1 (PAI-1). Treatment with ATRA in APL results in a rapid down-regulation of TF in APL promyelocytes and normalization of coagulation changes in blood in 4 to 5 days. Paradoxically, the use of ATRA is

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associated with thrombotic complications later in the course of the illness (in 1 to 3 weeks).⁵ Thromboembolic events in the form of deep vein thrombosis, portal vein thrombosis,⁶ and pulmonary embolism, as well as arterial thrombosis with splenic and renal infarction, have all been observed,⁷⁻⁹ mostly during induction therapy. When antifibrinolytic agents, epsilon-amino acid (Amicar), or tranexamic acid is given for hemostatic control, the risk of thrombosis is even greater.^{10,11} Because these antifibrinolytic agents have not been shown in clinical trials to be effective hemostatic agents in APL, they should not be used. There are multiple additional prothrombotic factors during chemotherapy. Because the leukemic promyelocytes express high levels of procoagulants, including TF and cancer procoagulant, any increased apoptosis of these cells, either as a result of the active leukemic process or induced by treatment with arsenic trioxide (ATO) or anthracycline therapy, can increase activation of TF.¹² Increased inflammatory cytokines, tumor necrosis factor α (TNF α), and interleukin-1 (IL-1) further augment the expression of TF in promyelocytes, endothelial cells, and monocytes. Another complication of ATRA or of ATO therapy is the occurrence of differentiation syndrome, formerly known as retinoic acid syndrome.¹³⁻¹⁵ In this syndrome, there is an interstitial infiltrate of maturing myeloid cells into the pulmonary alveoli. This may be associated with pronounced leukocytosis, which is known to be prothrombotic.

Antiangiogenic Agents

Neovascularization plays a key role in cancer biology. The growth, invasion, and development of both the primary tumor and its distant metastases is very much dependent on the development of new blood vessels.¹⁶ There are several

key epidermal growth factors and tyrosine kinases involved in neovascular formation, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor. This has led to interest in development of drugs specifically targeting tumor vessels, either as monoclonal antibodies directed against VEGF or indirectly as inhibitors of tyrosine kinases.

Bevacizumab is a humanized monoclonal antibody that inhibits VEGF activity. It has a therapeutic potential in the treatment of cancer, both directly and through enhancing other chemotherapeutics by overcoming tumor resistance. However, there is also the potential for significant toxicity, including severe bleeding and thrombotic events (**►Fig. 1**). These complications may be due to the fact that VEGF plays a role in normal endothelial function.^{16,17} Thrombotic complications may occur through exposure of prothrombotic factors following apoptosis of endothelial cells caused by bevacizumab. In addition, there is the potential for increasing platelet activation through blocking VEGF-induced production of prostaglandin I-2 and nitric oxide.¹⁸ This latter effect may increase the risk for arterial thrombotic events. Conversely, loss of endothelial integrity may result in bleeding and hemorrhagic complications.

There have been many clinical studies evaluating the safety and efficacy of bevacizumab in combination with chemotherapy in various malignancies, including colorectal, breast, lung, and renal cell carcinomas, as well as glioblastoma multiforme. In an earlier study by meta-analysis of 15 prospective randomized control trials involving a variety of solid tumors, patients given bevacizumab had a significant increased risk for venous thromboembolism (VTE) compared with those given standard chemotherapy alone.¹⁹ The overall rate of VTE

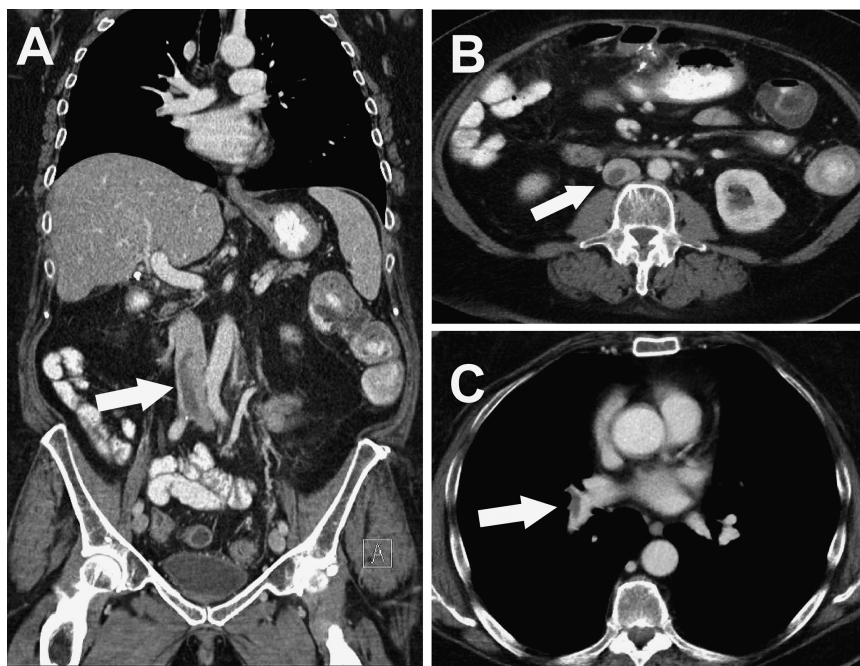


Fig. 1A–C Venous thromboembolism complicating bevacizumab treatment in a patient with colorectal carcinoma. Thrombus (white arrow) in the infrarenal portion of the inferior vena cava, coronal section (A) and axial section (B); embolus (white arrow) in right pulmonary artery, axial section (C).

in this study was 11.9% in those treated with bevacizumab. This, however, was not verified by a more recent meta-analysis evaluating VTE complications in 6,055 patients in 10 randomized studies utilizing bevacizumab, which failed to demonstrate an increased risk for VTE with use of the drug.²⁰ Although this study showed several factors including tumor type, patient age, performance status, and past history of VTE were associated with development of VTE, treatment with bevacizumab was not. The incidence in the control population was 9.8%, versus 10.9% in those given anti-VEGF therapy, with an overall odds ratio of 1.14 ($p = 0.13$). Interestingly, patients evaluated in this study who were given full-dose anticoagulation for their VTE had a low overall risk for severe bleeding ($< 1\%$), whether or not bevacizumab was given. Another meta-analysis evaluating fatal adverse events failed to show an association of bevacizumab with risk of fatal pulmonary embolism as well, with an overall incidence of 0.7% in those given bevacizumab versus 0.6% in controls, giving a relative risk of 1.10 ($p = 0.88$).²¹

Although VTE rates do not appear to be significantly increased with use of bevacizumab, arterial thrombotic events (ATE) have been shown to be higher, in the range of 1 to 3%.^{22,23} Rates of all-grade ATE were 3.3% and high-grade ATE 2.0% in a meta-analysis of over 12,000 patients with various advanced solid malignancies receiving bevacizumab.²³ These rates were higher when compared with those who only received standard chemotherapy (relative risk [RR] 1.4), and were similar with doses of 2.5 and 5 mg/kg/week. Of note, whereas risk of cardiac ischemia was higher with use of anti-VEGF therapy (RR 2.14), risk of ischemic stroke was not. Mechanism for ATE is not entirely clear, but may be related to increased platelet activation and endothelial damage attributed to the drug.

Even though there is concern for thrombotic complications with use of bevacizumab, there is also potential for significant bleeding. Rates of fatal hemorrhage were found to be 1.3% in a meta-analysis evaluating over 2,400 patients receiving the drug, which was significantly higher than controls (RR = 2.7 for fatal bleeding).²¹ Bevacizumab was also associated with a higher rate of fatal pulmonary hemorrhage in non-small cell lung cancer in this study. Although rates of fatal gastrointestinal bleeding were somewhat higher, the results were not statistically significant. It is noteworthy that the risk of hemorrhage was not higher in patients receiving aspirin for arterial thromboprophylaxis with bevacizumab use in a retrospective analysis of three trials.^{24,25} With such mixed results at this time, evaluation of potential thrombotic and bleeding risk with use of bevacizumab needs to be on an individual case-basis, incorporating the patients' comorbidities and clinical situation.

Antiangiogenic tyrosine kinase inhibitors have also been developed as therapeutic agents in oncology. One of the earliest to be studied clinically was semaxanib, an inhibitor of both VEGFR-1 and -2. However, development was stopped when high thrombotic rates were seen with semaxanib use in combination with other chemotherapeutic agents. When used with paclitaxel for recurrent or metastatic head and neck cancer, 25% of patients on a phase I study suffered VTE.²⁶

Similarly, another phase I study was terminated early after the first 8 of 19 patients enrolled (42%) developed thrombotic complications when semaxanib was used with gemcitabine and cisplatin for treatment of solid tumors.²⁷ Venous thrombotic issues have not been encountered to this degree with sunitinib or sorafenib, two other antiangiogenic tyrosine kinase inhibitors, particularly when used as single agents.²⁸ These agents are currently used to treat renal cell carcinoma, gastrointestinal stromal tumors, and hepatocellular carcinoma. However, there may be a small but significant increase in arterial thrombotic events, noting that cardiac ischemia occurred in 3% of patients on sorafenib compared with $< 1\%$ on placebo in a large randomized control trial of over 900 patients with advanced kidney cancer.²⁹ In addition, when sorafenib was used in combination with gemcitabine in a phase I study in solid tumors including pancreatic cancer, there was also a small increase in arterial thrombotic complications.³⁰

Cisplatin

Of the more traditional agents, cisplatin has the most clinical data regarding risk for thrombosis. This long-standing staple in many chemotherapeutic regimens used for multiple different tumor types has been associated with both venous and arterial thrombotic events. In one of the larger studies retrospectively evaluating over 900 patients who received cisplatin, approximately 18% of patients developed a thrombotic complication.³¹ The majority of these were venous, but 11% had an arterial component as well. These rates were very similar to a smaller, but prospective, study looking at cisplatin use together with gemcitabine in non-small cell lung cancer.³² The overall thrombotic rate was just under 18% in this study, with over 6% of these being arterial. The high risk for venous and arterial thrombosis in cisplatin-containing regimens in various malignancies has been found in other clinical studies as well, with reported rates similar to those already mentioned.^{33,34} Cisplatin appears to enhance thrombotic potential more than other chemotherapeutics, having been demonstrated to independently increase the risk in two separate studies evaluating different regimens in advanced gastroesophageal cancer.^{33,35} In both of these prospective studies, thrombotic complications were substantially higher in those patients who received cisplatin versus oxaliplatin-containing regimens for their GI cancer.

Estrogenic Hormones and Selective Estrogen Receptor Modifiers

The thrombotic risks associated with the use of these agents are discussed elsewhere in this issue of *Seminars in Thrombosis and Hemostasis* by Artero et al³⁶ and will not be reviewed here.

Gemtuzumab Ozagamicin (or Myelotag)

This drug is a conjugate of a humanized monoclonal antibody against the myeloid surface marker CD33 with a plant toxin calicheamicin. It is targeted to CD33 positive cells and after it is internalized and intracellularly released, it is highly toxic. It is used in acute myeloid leukemia^{37,38} and myelodysplastic

syndrome,^{39,40} either as a single agent or in combination with other chemotherapeutic agents.

Toxicity associated with this drug is mainly hematologic with cytopenias. Liver damage also occurs. A small number of patients developed venoocclusive disease (VOD), also known as sinusoidal obstruction syndrome. Hepatic venules and sinusoids in zone 3 of the hepatic acinus show subendothelial edema, fibrin deposition, and expression of von Willebrand factor.⁴¹ The incidence of gemtuzumab-associated VOD was reported to be 0.5% with single-agent therapy, but up to 5% when gemtuzumab was given in combination chemotherapy with hepatotoxic agents, particularly thioguanine. In patients who received hematopoietic stem cell transplantation subsequently or prior to gemtuzumab administration, the incidence of VOD is even higher, as much as 19%.^{42,43}

Glucocorticoids

The association between excessive corticosteroids and thrombosis was first observed in Cushing syndrome. During glucocorticoid administration, increased plasma levels of prothrombin, von Willebrand factor, and antithrombin, along with decreased fibrinogen and plasminogen, had been observed.⁴⁴ Glucocorticoid mediates apoptosis in tumor cells.⁴⁵ Dexamethasone in vitro activates caspase-9 enhancing apoptosis in myeloma cell line MM.1S.⁴⁶ Through this action, it can increase activation of tissue factor because apoptotic cells are more thrombogenic.¹² This agent is present in most chemotherapeutic regimens and can potentiate the thrombotic risk of these regimens, with a notable example seen when high dose of dexamethasone is given in with thalidomide.

Hematopoietic Growth Factors

Several chemotherapeutic regimens result in significant myelosuppression. Various hematopoietic growth factors have been developed to address this complication, with the primary goal of maintaining adequate peripheral blood counts during chemotherapeutic treatments, reducing the need for transfusion of blood products, and decreasing the morbidity associated with cytopenias, notably infection associated with neutropenia. Significant vascular complications have been associated with unrestricted use of the erythroid-stimulating agents (ESAs) in both the chemotherapy-associated anemia and the chronic kidney disease settings. Use of ESAs in cancer patients and in chronic kidney disease patients not on hemodialysis has now been curtailed. The complications associated with ESA use appear to be related to the dosing of ESAs, rather than the achieved hemoglobin level, and are discussed in detail by Bennett et al elsewhere in this issue of *Seminars in Thrombosis and Hemostasis*.⁴⁷

Thrombotic complications have rarely been associated with use of granulocyte-stimulating factor (G-CSF). Higher rates of thrombotic complications have been reported with granulocyte-macrophage stimulating factor (GM-CSF). G-CSF is frequently used with myeloablative chemotherapeutic regimens to reduce the risk of neutropenic infection and, in some instances, to treat febrile neutropenia. A meta-analysis of 52 reports involving over 1,800 patients showed a throm-

botic rate of 2.8%.⁴⁸ These included arterial and venous events, and the rates were higher with use of GM-CSF (4.2%) versus G-CSF (1.2%). This may be influenced by the transplant setting where GM-CSF is preferentially used. In patients undergoing chemotherapy for stem-cell transplantation, the incidence was 9.8% with GM-CSF versus 2.3% with G-CSF.⁴⁹ The underlying mechanism for this is not fully understood. G-CSF has been found to activate coagulation, increasing factor VIII levels, thrombin-antithrombin complexes, and prothrombin fragment F1 + 2 when given to healthy allogeneic stem-cell donors.⁵⁰ G-CSF also increases both tissue factor antigen and activity in donors.⁴⁹ In addition, GM-CSF increases neutrophil adhesion to the vascular endothelium. There is also an association between a high circulating leukocyte count and thrombotic risk.

Thrombocytopenia is a common complication of multi-agent chemotherapy as well. Clinical development of a recombinant form of human thrombopoietin (TPO) was abandoned after several patients receiving it developed refractory thrombocytopenia due to antibodies directed at TPO. More recently, TPO agonists without sequence homology with endogenous TPO have been developed and studied extensively for use in autoimmune thrombocytopenia (ITP). These agents include the peptide-mimetic romiplostim, as well as the nonpeptide-mimetic eltrombopag. Although they have not yet been sufficiently studied for use in cancer- or chemotherapy-induced thrombocytopenia, the potential for use in this area exists and raises concern for possibly further increasing the thrombotic risk in this patient population. This concern is born out of the potential for thrombocytosis with use of these agents. To date, the rates of thrombosis in patients receiving eltrombopag or romiplostim for ITP have not been significantly higher than those patients treated with placebo, even in some patients with platelet counts reaching > 500,000.^{51,52} Whether the risk for thrombosis would be higher with these agents if used in patients with cancer receiving chemotherapy has not been evaluated and would need to be carefully considered in evaluation for the safety of their use in this population.

L-Asparaginase

This bacteria-derived enzyme catalyzes the deamination of the amino acid asparagine. The latter is essential for the growth of lymphoid cells. Normal cells contain asparaginase synthetase and can be self-supporting. However, tumor cells lack this capability and depend on asparagine derived from circulating blood. Thus, L-asparaginase, by removing this amino acid from blood, becomes an effective drug for the treatment of lymphoid malignancies. After parenteral administration, circulating asparagine is rapidly depleted. Because this amino acid is also required for the hepatic synthesis of proteins, production of both coagulant and anticoagulants are affected. Plasma levels of the procoagulant factors, including fibrinogen; factors V, VII, VIII, IX, X, and XI; histidine-rich glycoprotein; α_2 -macroglobulin; and α_2 -antiplasmin are decreased. Likewise, there is a fall in the levels of anticoagulants including antithrombin, protein C, protein S, and plasminogen. Bleeding complications are not common despite the

coagulopathy and occur in the settings of concurrent thrombocytopenia. The prophylactic use of fresh frozen plasma, cryoprecipitate, or human fibrinogen concentrates is indicated when the plasma fibrinogen level is < 50mg/dL in the presence of thrombocytopenia. On the other hand, thrombotic complications are significant. In the Dana-Farber Cancer Institute regimen for acute lymphoblastic leukemia, the incidence of venous thromboembolic events in 548 patients was 8%.⁵³ The rate was higher in adults (34%) than in children (5%). A correlation was observed with more frequent thrombosis with advancing age group.

Methotrexate

One of the significant adverse drug reactions (ADRs) of methotrexate (MTX) is neurotoxicity, especially when given in high doses or given intrathecally. The neurotoxicity varies widely from mild headache to leukoencephalopathy.^{54,55} Thrombotic complications are uncommon except in cases when the patient has inherited methylene tetrahydrofolate reductase (MTHFR) C677T polymorphism.^{56,57} This polymorphism is found in 11% of children with acute lymphoblastic leukemia.⁵⁸ Another polymorphism of MTHFR is A1298C. The combined prevalence of C677T and A1298C polymorphism is present in > 10% of the healthy population.⁵⁹ The lack of MTHFR results in impaired methionine metabolism and leads to increased levels of homocysteine in blood and in cerebrospinal fluid.⁶⁰ The resulting increase in breakdown products of homocysteine, such as excitatory amino acids, leads to both neurotoxicity and endothelial damage. Because this polymorphism is not a rare hereditary thrombophilia, a greater awareness of this complication should be given to patients receiving high-dose MTX.

Thalidomide and Immune-Modulating Drugs (IMiDs)

Soon after thalidomide was first introduced into treatment regimens of multiple myeloma, increased thrombotic complications were found. An early survey of 10 phase II and phase III clinical trials of thalidomide in myeloma, renal cell carcinoma, prostate cancer, ovarian cancer, mantle cell

lymphoma, and glioblastoma revealed rates of thromboembolic events up to 43%.⁶¹ Subsequently, it became clear that the rate depends on the type of cancer, whether the drug was given singly or in combination with other drugs, and which therapeutic agents were given in the regimens. The incidence of VTE with different therapeutic regimens in myeloma is shown in **Table 1**. When thalidomide was given alone, the VTE rate is between 3 to 5% for both newly diagnosed or relapsed patients.⁶²⁻⁶⁵ However, in combination with other drugs, the rates were all higher and relative to the dose and number of doses of agents employed. With thalidomide and chemotherapy, the rate was 10 to 11%;^{66,67} with melphalan and prednisone, it was 6 to 17%⁶⁸⁻⁷⁰ but increased to 12 to 26% with given with high-dose dexamethasone (40 mg/day).^{62,71,72} The highest rate was seen when given with high-dose chemotherapy and prednisone.^{73,74} A similar pattern of thrombotic complications was seen with the analogue lenalidomide. Given alone, no thrombosis was observed in a clinical trial for myelodysplastic syndrome, confirming its lack of thrombogenic risk.⁷⁵ However, in myeloma, the rate was 19 to 75% when combined with high-dose dexamethasone⁷⁶ and lower at 8.5 to 16% at low-dose dexamethasone.⁷⁷

It is noteworthy that when the proteasome inhibitor bortezomib was given with either thalidomide or lenalidomide, the rate of thrombosis was reduced.⁷⁸ This protective effect is partly due to the pharmacologic properties of bortezomib. It prevents the degradation of p1κBα, an inhibitor of the transcription factor nuclear factor-κB (NFκB).^{79,80} The latter signals transcription of the fibrinolytic inhibitor, PAI-1.⁸¹ Thus, bortezomib indirectly promotes fibrinolysis. Inhibition of NFκB also blocks TF expression by cytokines. Platelet budding may be impaired, leading to transient thrombocytopenia and decreased platelet function.⁸² In addition, bortezomib increases the expression of thrombomodulin in endothelial cells.⁸³

These reported data are all derived from various clinical trials, designed primarily to evaluate the efficacy of the regimens and not specifically to assess thrombosis as an outcome. In many reports, there is no information on the

Table 1 Incidence of venous thromboembolism in myeloma without thromboprophylaxis

Drug combinations	Newly diagnosed cases	Relapse or refractory cases
Melphalan + prednisone	2–6% ^{68,69,104}	–
Dexamethasone (HD) alone	3% ⁶²	–
Thalidomide alone	3–4% ^{62,63}	2–5% ^{64,65}
Thalidomide + dexamethasone (HD)	12–26% ^{62,71,72}	–
Melphalan + prednisone + thalidomide	6–17% ^{68,69}	11% ¹⁰⁵
Thalidomide + chemotherapy	10–11% ^{66,67}	–
Thalidomide + high dose chemotherapy + prednisone	34% ⁷³	58% ⁷⁴
Lenalidomide alone	–	0% ¹⁰⁶
Lenalidomide + dexamethasone (HD)	19–75% ⁷⁶	11.4% ¹⁰⁷
Lenalidomide + dexamethasone (LD)	12% ⁷⁷	–

Abbreviations: HD, high dose; LD, low dose.

concurrent administration of drugs with prothrombotic risk, such as erythropoietin and GM-CSF. It is likely that in a nonclinical trial setting, the rate of thrombosis can be much higher depending on the individual risk of the patient, such as age and other comorbidities. Thromboprophylaxis is now the current standard of treatment. The International Myeloma Working Group recommended that these prophylactic measures should be prorated to the thrombotic risks.⁸⁴ For the low-risk patients receiving lenalidomide alone or with low-dose dexamethasone, aspirin 81 mg daily is recommended. On the other hand, for those patients receiving thalidomide, high-dose dexamethasone, or combinations with anthracyclines, aspirin is not effective and low molecular weight heparin (LMWH) or full-intensity warfarin regimen with INR 2–3 will be necessary. The duration of anticoagulation should be as long as the duration of therapy, which frequently is as long as 12 months from the time of diagnosis. In a recent meta-analysis, the rate of VTE was approximately halved when prophylaxis with LMWH or with warfarin was given with thalidomide regimens as a single drug or in combination with dexamethasone.⁸⁵ In the case of regimens using lenalidomide plus dexamethasone, the reduction in the incidence of thrombosis was also seen, although it was not as pronounced.

Combination Chemotherapy in Various Malignant Disorders

General Considerations

Multiple factors other than the chemotherapeutic agent contribute to the increased risk of thrombosis in cancer patients receiving chemotherapy. Cancer is a disease with many prothrombotic characteristics. The underlying malignant disorder may vary widely in its prothrombotic tendency.^{86,87} Among the solid tumors, carcinoma of stomach, brain, pancreas, breast, prostate, ovary, and adenocarcinoma of the lung carry a high risk of thrombosis, whereas acute promyelocytic leukemia, high-grade lymphoma, multiple myeloma, and myeloproliferative neoplasms are the most prothrombotic. Tumor cells frequently have high expression of procoagulants. Another determinant is whether the chemotherapeutic agent is given as a single drug or in combination. Other comorbid conditions include presence of infection, immobilization, and presence of inherited thrombophilia. Iatrogenic procedures, especially central venous catheters, are also major contributors to thrombotic complications. A good illustration of how all these factors influence the thrombotic risks can be seen in the two following cancers.

Carcinoma of the Breast

Thrombotic complications during the course of carcinoma of the breast are well recognized. Around 5 to 15% of patients developed VTE following chemotherapy.^{88–90} The administration of chemotherapy is not the only factor. Other contributory factors include a heavier tumor burden, with a higher incidence of 15% in advanced breast cancer.⁹¹ The addition of selective estrogen receptor modulators (SERMs), either in combination with chemotherapy or as adjuvant therapy,

results in higher incidence of thrombosis than when either is given alone.⁹² Aromatase inhibitors, on the other hand, are less thrombogenic than tamoxifen.⁹³ The recent addition of the antiangiogenic agent, bevacizumab, to the anti-breast cancer regimens poses another risk because this drug has been shown to increase the risk for arterial thrombosis in metastatic colorectal cancer, metastatic breast cancer, and non-small cell lung cancer, with incidence twice that when chemotherapy was given alone.⁹⁴ In other clinical trials, bevacizumab was found to increase the risk of VTE, with an RR of 1.33.⁹⁵ The biologic action of bevacizumab as an anti-vascular endothelial growth factor (VEGF) agent is complex,⁹⁶ resulting in endothelial damage and altered platelet function.

The mechanism by which chemotherapy causes thrombosis has also been investigated in breast cancer.^{97,98} A series of markers of coagulation in the plasma were studied before and sequentially for 3 months after chemotherapy. There was an increase in baseline levels of fibrinogen, D-dimer, tissue factor, and VEGF in those patients that developed VTE, whereas a D-dimer level of less than 500 ng/mL has a negative predictive value of 97%. Those with advanced cancer were found to have higher levels of these biomarkers. Other signs of activation of coagulation were found in increased thrombin-antithrombin complexes, tissue factor activity in microparticles, activated protein C, soluble thrombomodulin, and soluble endothelial protein C receptor.⁹⁸ Hopefully, some of these markers can be used for identifying high-risk patients that require thromboprophylaxis.

Multiple Myeloma

Both multiple myeloma and its precursor condition, monoclonal gammopathy of undetermined significance (MGUS), are associated with an increased risk of both arterial and venous thrombosis.^{99,100} Multiple risk factors have been identified. Some of these are reviewed in detail in the article by Zangari et al elsewhere in this issue of *Seminars in Thrombosis and Hemostasis*.¹⁰¹ Briefly, procoagulant factors, including von Willebrand factor and factor VIII, are increased along with inflammatory cytokines such as TNF α , IL-6, and C-reactive proteins. The latter cytokines enhance TF expression. The risk is higher in those patients with a higher tumor burden. In the actively proliferating myeloma, the rate of apoptosis is increased. This, in turn, facilitates TF activation.¹² Another factor is the presence of acquired or inherited thrombophilia. The most important factor, however, is the therapeutic regimen used, with the highest rate when high-dose chemotherapy is given with dexamethasone and thalidomide. These have been reviewed in an earlier section of this article.

The thrombotic complications are of major concern because they adversely affect not only the morbidity but also the survival of the patient. In a large study involving over 9,000 patients in Sweden, comparison was made between those with VTE and those without; the hazard ratio (HR) was 2.9 in the first year and still high 10 years later, whereas the HR of arterial thrombosis was 3.4 in the first year and 2.1 10 years later.¹⁰² There is thus a strong indication for use of thromboprophylaxis.

Conclusion

Thrombosis is a well-recognized complication in cancer patients. When chemotherapy is given, the risk of thromboembolic complications is greatly increased. The incidence varies with the specific malignancy, choice of drug regimen, and presence of other comorbid thrombophilia. In most cases, the mechanisms of thrombogenesis are still not clearly elucidated, and further investigation is needed. Clarifying the underlying mechanism may prove helpful not only in identifying those cancer patients who may be at highest risk for thrombotic complications but also for understanding why they tend to have a worse overall prognosis. Until that time, there are certain settings in oncology where VTE prophylaxis is strongly recommended, as outlined in the article by Maxwell and Bennett in this issue of *Seminars in Thrombosis and Hemostasis*.¹⁰³

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