Adverse Effects on Hemostatic Function of Drugs Used in Hematologic Malignancies

Anaadriana Zakarija, M.D.,[1] and Hau C. Kwaan, M.D., Ph.D.[1]

ABSTRACT

The adverse effects of drugs used in the treatment of hematologic malignancies are among the many factors contributing to the increased risk of both thrombosis and bleeding. These effects most often occur when combination of drugs are given. Some, such as L-asparaginase, result in both bleeding and thrombosis. Consideration must be given also to the bleeding or prothrombotic risk of the underlying hematologic disorder. The commonly used drugs with adverse effects on hemostasis include L-asparaginase, corticosteroids, inhibitors of vascular endothelial growth factor, gemtuzumab ozogamicin, thalidomide, and immunomodulatory derivatives of Thalidomide, and the hematopoietic growth factors. In addition, the syndrome of thrombotic microangiopathy may be brought on by several other drugs. Thus, a full understanding of these adverse effects is necessary in treating these disorders.

KEYWORDS: Leukemia, myeloma, thalidomide, L-asparaginase, growth factors, thrombosis

Thromboembolic events (TEEs) are well recognized to contribute significantly to complications during the treatment of hematologic malignant disorders. Several factors must be taken into consideration. The individual disorders per se have characteristics that predispose to TEEs. In addition, many therapeutic drugs have also prothrombotic properties. If the medications are used as a single drug or in combination, the risk of TEEs can be magnified to varying degrees. To add to the complexity, the effect of a particular drug may be sequential, with bleeding risk at one time and prothrombotic risk at another, as exemplified by the case of L-asparaginase. This review discusses both the effects of these combined factors and the specific drug actions.

L-ASPARAGINASE

This antitumor agent has been studied extensively regarding its profound effect on the coagulation and fibrinolytic systems. This drug acts on the essential amino acid L-asparagine, which is essential for cell growth, particularly in lymphocytes, and converts it to aspartic acid. Normal cells contain L-asparagine synthetase and can be self-supporting. However, tumor cells lack this enzyme and depend on circulating blood to provide this amino acid. Thus, by depleting circulating L-asparagine, tumor growth is inhibited. Adverse effects of this drug include hypersensitivity reactions, ranging in severity from drug rash to anaphylaxis, and impaired protein synthesis, including albumin, procoagulant and anticoagulant factors as well as several components of the fibrinolytic system. The impaired protein synthesis results in the lowering of plasma levels of fibrinogen, factor (F) V, FVII, FVIII, FIX, FX, FXI, histidine-rich glycoprotein, α_2-macroglobulin, and α_2-antiplasmin. During treatment there is an increased bleeding risk, although the overall incidence of bleeding complications is low. One reason for this low

[1]Division of Hematology/Oncology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

Address for correspondence and reprint requests: Hau C. Kwaan, M.D., Division of Hematology/Oncology, Feinberg School of Medicine, Northwestern University, 303 East Chicago Ave., Chicago, IL 60611. E-mail: h-kwaan@northwestern.edu.

Hemostatic Dysfunction in Malignant Hematologic Disorders; Guest Editor, Hau C. Kwaan, M.D., Ph.D.

Semin Thromb Hemost 2007;33:355–364.
DOI 10.1055/s-2007-976171. ISSN 0094-6176.

incidence is the concurrent impaired synthesis of the naturally occurring anticoagulant proteins, including antithrombin, protein C, protein S, and plasminogen. The balance is tilted further toward a prothrombotic tendency after the cessation of L-asparaginase therapy, when the recovery of the coagulant proteins (fibrinogen, FVII) takes place earlier than the recovery of the anticoagulant proteins. In addition, an increased endogenous thrombin generation has been documented in children with acute lymphoblastic leukemia (ALL) at presentation and throughout the course of therapy.[1]

Clinically, L-asparaginase is used in several treatment protocols for ALL, and is used in various combinations with prednisone, daunorubicin, vincristine, cytarabine, cyclophosphamide, methotrexate, and thioguanine.[2,3] In most treatment protocols, L-asparaginase is administered following several days of prednisone therapy, which has already reduced the fibrinogen level. Thus, the hypofibrinogenemic effect of L-asparaginase can be quite pronounced. Laboratory monitoring of the plasma fibrinogen, prothrombin time, and partial thromboplastin time should be done routinely. Cryoprecipitates are given when severe hypofibrinogenemia, with levels of 100 mg/dL or less, develops. The bleeding risk is accentuated further if there is concurrent thrombocytopenia, which may require additional platelet transfusion. Following this phase of therapy, the prothrombotic risk increases. Earlier studies placed the incidence of thromboembolic complications of L-asparaginase therapy to be approximately 2 to 10%. However, in a recent prospective study of 60 children treated for ALL with L-asparaginase, a much higher rate of 36.7% was found.[2,3] Most thromboses were asymptomatic and occurred in the upper extremities, suggesting that the use of central venous access catheters may be a contributory factor. Others have reported intracranial thrombotic and hemorrhagic complications[4,5]; the former were sinus venous thrombosis and the latter were cerebral hemorrhages. When thrombotic complications occur and require thrombolytic therapy with plasminogen activators, the supplementation of plasminogen may be necessary because the patient's plasminogen level may be low.[6]

GLUCOCORTICOIDS

The increased risk for thrombosis has long been known in patients with Cushing syndrome. The effect is likely due to the high plasma levels of glucocorticoids. Earlier studies revealed that prednisone treatment resulted in increased plasma levels of prothrombin, von Willebrand factor, and antithrombin, along with decreased fibrinogen and plasminogen.[7,8] These changes have been confirmed recently when prednisone is used during chemotherapy for ALL. In the first phase of therapy, following 5 days of prednisone, there is a decrease in the plasma fibrinogen level.[2] Thus, when L-asparaginase is administered in the next phase of the therapy, the hypofibrinogenemic effect of this drug is enhanced. On the other hand, the thrombotic risk is increased when corticosteroids are used in other chemotherapeutic combinations. Among 60 cancer patients who received thalidomide and dexamethasone, including those with myeloma, lymphoma, and renal cell carcinoma, nine (15%) developed thromboembolic complications, including eight with deep venous thromboses and one with a pulmonary embolus. Among 326 cancer patients who received thalidomide alone, 15 (5%) developed thromboembolic complications, including 10 with deep venous thromboses, one with a pulmonary embolus, and four with both a deep venous thrombosis and a pulmonary embolus.[9] Similar findings are seen when corticosteroids are used for anticancer treatment with chemotherapy combinations. The thrombogenic effect of dexamethasone in myeloma is discussed in the section entitled "Thalidomide and Immunomodulatory Derivatives."

VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS

Several antiangiogenic compounds have been developed in recent years. Many of these are inhibitors of vascular endothelial growth factor (VEGF) or its receptors. By blocking VEGF activities, these compounds may interfere with endothelial cell function and thus thrombosis can result. Most reports on increased thrombotic complications are with bevacizumab (Avastin; Genentech, Inc.; South San Francisco, CA), a monoclonal antibody against VEGF. When used in combination with various chemotherapeutic agents in multiple solid tumors, including carcinoma of the colon, lung, or ovary, an increased incidence of TEEs was noted: 13 to 26% in the bevacizumab arm versus 9% in the control arm.[10,11] In a series of 813 patients with metastatic colorectal carcinoma, roughly half of the patients were treated with chemotherapy (irinotecan, 5-fluorouracil [5-FU] plus leucovorin) alone and the rest received chemotherapy plus bevacizumab. The incidence of all thrombotic events was higher in the bevacizumab plus chemotherapy group (19.4%) when compared with the chemotherapy-alone group (16.2%), although this difference did not reach statistical significance ($p = 0.26$).[12] Thrombotic events noted in several clinical trials have included deep venous thrombosis, pulmonary embolism, catheter-associated thrombosis, cerebrovascular events, and transient ischemic events. Independent risk factors for arterial thrombotic events with bevacizumab and chemotherapy are a history of atherosclerosis or age older than 65 years[13]; therefore, this agent should be used in caution in this population.

VEGF modulates endothelial cell function including increased permeability, proliferation, and migration,[14] and has been shown to induce rapid release of von Willebrand factor; increase the expression of tissue factor

(TF), thrombomodulin, plasminogen activators (tissue-type plasminogen activator and urokinase-type plasminogen activator), plasminogen activator inhibitor type 1, and urokinase plasminogen activator receptor; and to promote adhesion and activation of platelets.[15] Thus, effective inhibition of VEGF activity theoretically could cause both bleeding and thrombosis.[16] In fact, increased bleeding was seen in one phase II trial of bevacizumab in metastatic renal cell carcinoma with statistically higher rates of epistaxis, hematuria, and hemoptysis ($p \leq 0.05$).[17] This bleeding risk was also demonstrated in a phase III study of 878 patients with advanced non–small-cell lung cancer who were randomly assigned to receive paclitaxel plus carboplatin alone or with bevacizumab. The group that received bevacizumab had a 4.4% incidence of grade 3 or higher bleeding, whereas the rate was only 0.7% in the chemotherapy-alone group ($p < 0.001$).[18] The bleeding events in the bevacizumab group included five fatal pulmonary hemorrhages and two fatal gastrointestinal hemorrhages.[18]

Another anti-VEGF peptide, SU5416, which is a tyrosine kinase inhibitor of VEGF receptor-2, was found to cause endothelial cell activation, and is prothrombotic when administered with cisplatin and gemcitabine.[19–21] The combination with cisplatin contributes to the thrombogenicity, given that cisplatin can cause platelet activation, an increase in von Willebrand factor, and vasospasm.[22] Because of the double hazard of thrombosis and bleeding with the VEGF inhibitors, the prophylactic use of anticoagulants should be viewed with caution.

GEMTUZUMAB OZOGAMICIN

Gemtuzumab ozogamicin (OG; Mylotarg; Wyeth; Madison, WI) is an immunoconjugate consisting of a humanized monoclonal antibody against CD33 conjugated with a cytotoxic agent calicheamicin. It was developed for the treatment of acute myeloid leukemia with CD33-positive myeloblasts.[23] Hepatic veno-occlusive disease (VOD) was reported in 0.9% of patients treated with GO alone for acute myeloid leukemia, but the incidence increased to 5% when administered with other chemotherapeutic agents, and was 19% in those treated after hematopoietic stem-cell transplantation.[24] Other reports showed an incidence of 12%[25] in those who did not undergo stem-cell transplantation. Given that hepatic toxicity with GO is quite common, occurring in as many as half of the patients, Nabhan et al[26] pointed out that VOD may be overdiagnosed if specific imaging studies are not performed. Hepatic vein occlusion (Budd-Chiari syndrome) has also been reported in patients treated with GO.[27] The subject of GO-associated sinusoidal obstruction syndrome, formerly known as VOD, has been reviewed recently.[28,29] The mechanism of this unusual toxicity is not clear. Several possibilities have been postulated, including free radical damage due to glutathione deficiency,[30] or endothelial cell activation associated with inflammatory cytokines.[29] It also has been shown that CD33 is not expressed in human umbilical vein endothelial cells in culture,[31] but whether this is also the case with hepatic sinusoidal endothelial cells is not known.

THALIDOMIDE AND IMMUNOMODULATORY DERIVATIVES

Following the tragic teratogenic effects on newborns, thalidomide was withdrawn in 1962 but was reintroduced into the therapeutic armamentarium in 1998, initially for leprosy and subsequently for various hematologic malignancies, especially multiple myeloma.[32–34] Among the major adverse effects are TEEs.[9,35–38] When used alone in myeloma, the incidence is approximately 1 to 2%,[34,39] but the rate increases to as much as 27% when combined with dexamethasone,[35,40] and is even higher when an anthracycline drug (doxorubicin) is added to the chemotherapy regimen.[36] This complication also occurs when thalidomide is used in the treatment of mantle cell lymphoma, glioblastoma, melanoma, renal cell carcinoma, hepatocellular carcinoma, carcinoma of prostate or ovary, and for the myelodysplastic syndrome, with rates from 17 to 43% (again higher when given in combination with chemotherapeutic agents). The thromboembolic incidence in the lenalidomide plus dexamethasone combination therapy was reported to be lower (3%) in a small series[41,42] but was found to be 10 to 15% in larger clinical trials.[42,43]

This alarming incidence has led to the use of prophylactic anticoagulation during the treatment using low-dose aspirin[44] or low molecular weight heparin.[45]

A better understanding of the causative factors for thrombosis has been made possible by recent knowledge of the pathogenesis of myeloma as well as the mechanism of action of Thalidomide/immunomodulatory derivatives (IMiDs).[46–53] In the microenvironment of bone marrow in myeloma, the key players include the myeloma cells, bone marrow stromal cells, microvascular endothelial cells, and $CD8^+$ T cells and natural killer (NK) cells.[46,53,54] Myeloma cells adhere to the stromal cells, which prevent apoptosis and secrete the growth stimulatory factor and survival factor interleukin-6 (IL-6).[55] Myeloma cells secrete cytokines including tissue necrosis factor alpha, transforming growth factor beta, and VEGF.[48,56,57] These, in turn, affect the stromal cells upregulating IL-6 secretion and promoting angiogenesis[48] and myeloma cell migration.[58] Thalidomide/IMiDs act by interdicting the above-described steps, including promoting apoptosis by blocking the adhesion of myeloma cells to stromal cells, inhibiting the myeloma secretion of cytokines, blocking drug resistance, and upregulating the patient's immune apparatus

(NK cells, $CD8^+$ T lymphocytes) against the myeloma cells and increasing cell kill by antibody-dependent cellular cytotoxicity. The recently approved IMiD, lenalidomide, has a mode of action similar to that of Thalidomide, but is more potent in several respects including augmenting of T-cell activity, inhibiting angiogenesis, and overcoming drug resistance.[47] Some of these actions are relevant to thrombogenesis. During apoptosis the procoagulant TF on the cell membrane is activated by phosphatylserine,[59] rendering apoptotic cells more thrombogenic. The thrombogenic potentiation of VEGF inhibition is discussed in the section entitled Vascular Endothelial Growth Factor Inhibitors. In addition, the normal regulation of the coagulation system is likely impaired, given that plasma thrombomodulin levels are found to be low during the first month of treatment with thalidomide and dexamethasone.[60] Finally, other prothrombotic characteristics in myeloma include newly diagnosed disease, chromosome 13 abnormalities, older age, high lactate dehydrogenase level, and high creatinine level.[61]

ALL-*TRANS* RETINOIC ACID

In acute promyelocytic leukemia (APL), the chromosomal translocation t(15;17) results in the formation of the fusion proteins PML-RARα or PLZF-RARα.[62–68] In the absence of retinoic acid, these proteins bind to the RARα target genes and form heterodimers with RXR and corepressors, leading to failure of differentiation of cells of the myeloid lineage and resulting in the development of APL. All-*trans* retinoic acid (ATRA) induces the dissociation of the nuclear corepressors and enables the transcriptional activation and induction of differentiation. APL cells expressing (PLZF-RARα) fusion protein are resistant to ATRA but may respond to arsenic trioxide. Treatment with ATRA in APL results in the resolution of the coagulopathy and bleeding induced by disseminated intravascular coagulation that frequently is evident at the time of APL presentation, but paradoxically induces thrombosis in a small number of patients. This was first observed by Schneider[69] and Runde et al.[70] The prothrombotic complications should be distinguished from retinoic acid syndrome, characterized by hyperleukocytosis, and extravasation of leukocytes especially in pulmonary alveoli, which occurs in 4 to 26% of ATRA-treated APL patients.[71–73] In ATRA-associated thrombosis, the complication occurs 1 to 3 weeks following the treatment, at a time when the coagulopathy has been corrected,[70,74] and can involve multiple organs including heart, brain, lungs, and spleen.[74–76] Antifibrinolytic agents, such as tranexemic acid, have also been shown to increase the risk of this potentially fatal complication,[77,78] and thus are contraindicated. Various thrombogenic factors have been proposed, including the induction of apoptosis by ATRA,[79] upregulation of adhesive molecules, and increased production of cytokines.[80] It is interesting that arsenic trioxide, which also causes apoptosis and cell differentiation in APL by degradation of the PML-RARα fusion protein, is not associated with significant TEEs, although hyperleukocytosis occurs.[81–83]

ERYTHROPOIETIN

Recombinant human erythropoietin is available in the United States as epoetin alfa (Procrit, Epogen) or darbepoetin alfa (Aranesp). Other products that are not available in the United States include epoetin alfa (Eprex) and epoetin β (NeoRecormon). The indications for products approved by the U.S. Food and Drug Administration (FDA) include the treatment of anemia in patients with solid tumors or nonmyeloid malignancies, and the first was approved in 1993. Darbepoetin, initially approved in 2001, has a different amino acid sequence and increased degree of glycosylation, which results in a longer half-life. The erythropoietin products are effective at improving the hemoglobin and decreasing transfusion requirements.[84]

Epoetin was initially approved for the treatment of anemia in patients with chronic renal disease. In this population early reports suggested that patients who received epoetin had a hematologic improvement but had a higher mortality with a higher target hemoglobin.[85] Two recent studies in patients with chronic renal disease were performed to assess optimal target hemoglobin.[86,87] There was no evidence that a higher hemoglobin level increased the risk of vascular or thrombotic events; however, overall mortality was higher, with higher target hemoglobin in one of the studies.[87] Conversely, a meta-analysis report on 6769 cancer patients in 35 trials treated with epoetin alfa and β (i.e., epoetin) and darbepoetin alfa (i.e., darbepoetin), suggests that the thrombotic risk is increased.[84] TEEs occurred in 229 of 3728 patients treated with erythropoietin, compared with 118 of 3041 patients who did not.[84] This was a statistically significant difference, with a relative risk of 1.67 (95% confidence interval, 1.35 to 2.06).

It is possible that some of the thrombotic risk may be due to a higher hemoglobin level. In data presented to the FDA, three studies of epoetin alfa with a goal to achieve hemoglobin > 13 g/dL were stopped early due to increased incidence of thrombosis. In these studies, 24 of 34 patients with a vascular events while treated with epoetin had a hemoglobin > 13 g/dL in the 28 days prior to the event.[88] Conversely, the thrombotic risk may be independent of hemoglobin level. Epoetin alfa administered to normal healthy volunteers three times a week for 2 weeks resulted in a 10 to 20% increase in platelet count on day 5, and elevated P-selectin and E-selectin levels.[89] This evidence suggests that erythropoietin alone

may increase thrombogenicity due to increased platelet reactivity or endothelial cell activation.[89]

The thrombogenic risk is not limited to patients with high hemoglobin levels, but is present in hematologic disorders with high thrombotic risk especially when a drug with thrombogenic potential is administered. In a phase II trial conducted in patients with low- or intermediate-risk myelodysplastic syndrome (MDS) treated with a combination regimen of thalidomide and darbepoetin, three patients developed either a deep vein thrombosis or pulmonary embolism, including one fatal event, necessitating the termination of the trial.[37] The events occurred 6 to 11 weeks after the start of therapy, and did not occur in association with a high hemoglobin. Prior studies have not found an increased rate of thrombotic events when either erythropoietin[90] or Thalidomide[91] alone was used in the treatment of MDS.

Because of the potential thrombogenicity of the growth factors, these agents should be used cautiously. An American Society of Hematology/American Society of Clinical Oncology guideline panel suggests the use of recombinant erythropoietin in MDS, whereas in hematologic malignancies the panel recommends that treatment of the underlying malignancy should be foremost, and use of erythropoietin should be considered only if anemia does not respond to tumor-specific treatment.[92] If erythropoietin products are used, then careful monitoring of hemoglobin is important, and the dose should be withheld if hemoglobin is > 12 g/dL.

GRANULOCYTE-COLONY STIMULATING FACTOR/GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR

Recombinant granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are used in cancer patients to shorten the duration of neutropenia and decrease the risk of febrile neutropenia (Amgen, Inc.; Thousand Oaks, CA). In addition, these hematopoietic growth factors are administered to normal healthy donors to facilitate peripheral stem-cell collection. Thrombotic events have been described in patients with malignancy receiving either G-CSF (Neupogen) or GM-CSF (Leukine; BerlexLab; Montville, NJ).[93] Barbui et al[93] reviewed 52 articles describing 1846 patients who received G-CSF or GM-CSF during treatment for both solid tumor and hematologic malignancies. Thrombotic events, both arterial and venous, occurred in 2.8% of all patients. The incidence was 4.2% with GM-CSF and 1.2% with the use of G-CSF. The primary outcome of these studies was not thrombotic events and therefore it is likely that the incidence was underestimated. The highest risks were found in patients with metastatic gastrointestinal adenocarcinoma who received GM-CSF concurrently with 5-FU, in whom the incidence of thrombotic events was 14%.[94] The risk of thrombosis was also increased in patients undergoing chemotherapy for stem-cell transplantation and appeared to be higher with the use of GM-CSF (9.8%) compared with G-CSF (2.3%).[93]

G-CSF has been found to increase markers of coagulation activation, including FVIII levels, thrombin–antithrombin complexes, and prothrombin fragment F1 + 2 in normal allogeneic stem-cell donors.[95,96] In addition, G-CSF increases both TF antigen and activity in normal donors after 5 days of G-CSF administration.[97] It is not clear how much these changes contribute to the thrombogenic mechanism, but clinicians should be aware of the potential for thrombotic complications with these agents.

DRUG-ASSOCIATED THROMBOTIC MICROANGIOPATHIES

A variety of medications have been associated with the development of thrombotic thrombocytopenic purpura (TTP) or hemolytic-uremic syndrome (HUS; Table 1).[98–100] Given the overlap between these clinical entities, particularly when they are secondary to a drug or other condition, the term thrombotic microangiopathy (TMA) has been adopted. The most commonly reported agents associated with TMA include mitomycin-C, quinine, cyclosporine, and ticlopidine.[100] Additional drugs used in the treatment of hematologic malignancies that have been implicated include daunorubicin, cytarabine, bleomycin, cisplatin, deoxycoformycin (pentostatin), arsenic, α-interferon,[101,102] and gemcitabine.[103] In addition, patients undergoing hematopoietic stem-cell transplantation (HSCT) can develop a thrombotic microangiopathy, which may be due to exposure to calcineurin inhibitors (cyclosporin or tacrolimus). The two proposed mechanisms by which a drug leads to TMA include immune-mediated effect or a direct toxic effect.[100] Recent TTP case series demonstrate that most drug-associated TTP cases are not associated with a severe ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type 1 motifs) deficiency or with the presence of an ADAMTS13 inhibitor.[104–106]

Table 1 Drugs Associated with TTP/HUS

Chemotherapeutic Agents	Others
Mitomycin-C	Quinine/quinidine
Gemcitabine	Ticlopidine
Daunorubicin	Clopidogrel
Cytarabine	Tacrolimus
Bleomycin	Cyclosporine
Cisplatin	Interferon-α
Arsenic	
Deoxycoformycin	

TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome.

with acute lymphoblastic leukemia: risk of thrombotic complications in L-asparaginase-induced antithrombin III deficiency. Blood 1994;83:386–391
2. Mitchell L, Andrew M, Hanna K, et al. Trend to efficacy and safety using antithrombin concentrate in prevention of thrombosis in children receiving L-asparaginase for acute lymphoblastic leukemia. Results of the PAARKA study. Thromb Haemost 2003;90:235–244
3. Mitchell LG, Halton JM, Vegh PA, et al. Effect of disease and chemotherapy on hemostasis in children with acute lymphoid leukemia. Am J Pediatr Hematol Oncol 1994; 16:120–126
4. Kieslich M, Porto L, Lanfermann H, Jacobi G, Schwabe D, Bohles H. Cerebrovascular complications of L-asparaginase in the therapy of acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2003;25:484–487
5. Fleischhack G, Solymosi L, Reiter A, Bender-Gotze C, Eberl W, Bode U. Imaging methods in diagnosis of cerebrovascular complications with L-asparaginase therapy. Klin Padiatr 1994;206:334–341
6. Kucuk O, Kwaan HC, Gunnar W, Vazquez RM. Thromboembolic complications associated with L-asparaginase therapy. Etiologic role of low antithrombin III and plasminogen levels and therapeutic correction by fresh frozen plasma. Cancer 1985;55:702–706
7. Isacson S. Effect of prednisolone on the coagulation and fibrinolytic systems. Scand J Haematol 1970;7:212–216
8. Jorgensen KA, Sorensen P, Freund L. Effect of glucocorticosteroids on some coagulation tests. Acta Haematol 1982; 68:39–42
9. Bennett CL, Schumock GT, Desai AA, et al. Thalidomide-associated deep vein thrombosis and pulmonary embolism. Am J Med 2002;113:603–606
10. Ratner M. Genentech discloses safety concerns over Avastin. Nat Biotechnol 2004;22:1198
11. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. Phase II. randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003;21:60–65
12. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–2342
13. Skillings JR, Johnson DH, Miller K, et al. Arterial thromboembolic events (ATEs) in a pooled analysis of 5 randomized, controlled trials of bevacizumab with chemotherapy. J Clin Oncol 2005;23(suppl 1):196s (abst 3019)
14. Pinedo HM. The role of VEGF in oncology: effects on hemostasis and thrombosis. Pathophysiol Haemost Thromb 2003;33(suppl 1):11–12
15. Verheul HM, Jorna AS, Hoekman K, Broxterman HJ, Gebbink MF, Pinedo HM. Vascular endothelial growth factor-stimulated endothelial cells promote adhesion and activation of platelets. Blood 2000;96:4216–4221
16. Kilickap S, Abali H, Celik I. Bevacizumab, bleeding, thrombosis, and warfarin. J Clin Oncol 2003;21:3542–3543
17. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003; 349:427–434
18. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–2550
19. Kuenen BC, Levi M, Meijers JC, et al. Potential role of platelets in endothelial damage observed during treatment with cisplatin, gemcitabine, and the angiogenesis inhibitor SU5416. J Clin Oncol 2003;21:2192–2198
20. Kuenen BC, Levi M, Meijers JC, et al. Analysis of coagulation cascade and endothelial cell activation during inhibition of vascular endothelial growth factor/vascular endothelial growth factor receptor pathway in cancer patients. Arterioscler Thromb Vasc Biol 2002;22:1500–1505
21. Marx GM, Steer CB, Harper P, Pavlakis N, Rixe O, Khayat D. Unexpected serious toxicity with chemotherapy and antiangiogenic combinations: time to take stock!. J Clin Oncol 2002;20:1446–1448
22. Icli F, Karaoguz H, Dincol D, et al. Severe vascular toxicity associated with cisplatin-based chemotherapy. Cancer 1993; 72:587–593
23. Bross PF, Beitz J, Chen G, et al. Approval summary: gemtuzumab ozogamicin in relapsed acute myeloid leukemia. Clin Cancer Res 2001;7:1490–1496
24. Larson RA, Sievers EL, Stadtmauer EA, et al. Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. Cancer 2005;104:1442–1452
25. Giles FJ, Kantarjian HM, Kornblau SM, et al. Mylotarg (gemtuzumab ozogamicin) therapy is associated with hepatic venoocclusive disease in patients who have not received stem cell transplantation. Cancer 2001;92:406–413
26. Nabhan C, Rundhaugen L, Jatoi M, et al. Gemtuzumab ozogamicin (Mylotarg™) is infrequently associated with sinusoidal obstructive syndrome/veno-occlusive disease. Ann Oncol 2004;15:1231–1236
27. Kurt M, Shorbagi A, Altundag K, Elkiran T, Gullu I, Kansu E. Possible association between Budd-Chiari Syndrome and gemtuzumab ozogamicin treatment in a patient with refractory acute myelogenous leukemia. Am J Hematol 2005;80:213–215
28. McKoy JM, Angelotta C, Bennett CL, et al. Gemtuzumab ozogamicin-associated sinusoidal obstructive syndrome (SOS): An overview from the research on adverse drug events and reports (RADAR) project. Leuk Res 2006; September 7(Epub ahead of print)
29. DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). Semin Liver Dis 2002;22:27–42
30. Gordon LI. Gemtuzumab ozogamicin (Mylotarg) and hepatic veno-occlusive disease: take two acetaminophen, and... Bone Marrow Transplant 2001;28:811–812
31. Favaloro EJ. Differential expression of surface antigens on activated endothelium. Immunol Cell Biol 1993;71(pt 6): 571–581
32. Dimopoulos MA, Eleutherakis-Papaiakovou V. Adverse effects of thalidomide administration in patients with neoplastic diseases. Am J Med 2004;117:508–515
33. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med 2004;351:1860–1873
34. Singhal S, Mehta J. Thalidomide in cancer. Biomed Pharmacother 2002;56:4–12
35. Osman K, Comenzo R, Rajkumar SV. Deep venous thrombosis and thalidomide therapy for multiple myeloma. N Engl J Med 2001;344:1951–1952
36. Zangari M, Siegel E, Barlogie B, et al. Thrombogenic activity of doxorubicin in myeloma patients receiving

thalidomide: implications for therapy. Blood 2002;100: 1168–1171
37. Steurer M, Sudmeier I, Stauder R, Gastl G. Thromboembolic events in patients with myelodysplastic syndrome receiving thalidomide in combination with darbepoetin-alpha. Br J Haematol 2003;121:101–103
38. Desai AA, Vogelzang NJ, Rini BI, Ansari R, Krauss S, Stadler WM. A high rate of venous thromboembolism in a multi-institutional phase II trial of weekly intravenous gemcitabine with continuous infusion fluorouracil and daily thalidomide in patients with metastatic renal cell carcinoma. Cancer 2002;95:1629–1636
39. Barlogie B, Desikan R, Eddlemon P, et al. Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients. Blood 2001;98:492–494
40. Cavo M, Zamagni E, Cellini C, et al. Deep-vein thrombosis in patients with multiple myeloma receiving first-line thalidomide-dexamethasone therapy. Blood 2002;100: 2272–2273
41. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood 2005;106:4050–4053
42. Rajkumar SV, Blood E. Lenalidomide and venous thrombosis in multiple myeloma. N Engl J Med 2006;354:2079–2080
43. Zonder JA, Barlogie B, Durie BG, McCoy J, Crowley J, Hussein MA. Thrombotic complications in patients with newly diagnosed multiple myeloma treated with lenalidomide and dexamethasone: benefit of aspirin prophylaxis. Blood 2006;108:403 (author reply 404)
44. Baz R, Li L, Kottke-Marchant K, et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. Mayo Clin Proc 2005;80:1568–1574
45. Zangari M, Barlogie B, Anaissie E, et al. Deep vein thrombosis in patients with multiple myeloma treated with thalidomide and chemotherapy: effects of prophylactic and therapeutic anticoagulation. Br J Haematol 2004;126:715–721
46. Anderson KC. The role of immunomodulatory drugs in multiple myeloma. Semin Hematol 2003;40:23–32
47. Anderson KC, Prince HM. Lenalidomide and thalidomide: an evolving paradigm for the management of multiple myeloma. Semin Hematol 2005;42:S1–S2
48. Podar K, Tai YT, Davies FE, et al. Vascular endothelial growth factor triggers signaling cascades mediating multiple myeloma cell growth and migration. Blood 2001;98:428–435
49. Davies FE, Raje N, Hideshima T, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. Blood 2001;98:210–216
50. Hideshima T, Chauhan D, Shima Y, et al. Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood 2000;96: 2943–2950
51. Gupta D, Treon SP, Shima Y, et al. Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications. Leukemia 2001;15:1950–1961
52. Lentzsch S, LeBlanc R, Podar K, et al. Immunomodulatory analogs of thalidomide inhibit growth of Hs Sultan cells and angiogenesis in vivo. Leukemia 2003;17:41–44
53. Anderson KC. Moving disease biology from the lab to the clinic. Cancer 2003;97:796–801
54. Anderson KC, Pazdur R, Farrell AT. Development of effective new treatments for multiple myeloma. J Clin Oncol 2005;23:7207–7211
55. Chauhan D, Uchiyama H, Akbarali Y, et al. Multiple myeloma cell adhesion-induced interleukin-6 expression in bone marrow stromal cells involves activation of NF-kappa B. Blood 1996;87:1104–1112
56. Urashima M, Ogata A, Chauhan D, et al. Transforming growth factor-beta1: differential effects on multiple myeloma versus normal B cells. Blood 1996;87:1928–1938
57. Hideshima T, Chauhan D, Schlossman R, Richardson P, Anderson KC. The role of tumor necrosis factor alpha in the pathophysiology of human multiple myeloma: therapeutic applications. Oncogene 2001;20:4519–4527
58. Hideshima T, Chauhan D, Richardson P, Anderson KC. Identification and validation of novel therapeutic targets for multiple myeloma. J Clin Oncol 2005;23:6345–6350
59. Kwaan HC, Parmar S, Wang J. Pathogenesis of increased risk of thrombosis in cancer. Semin Thromb Hemost 2003; 29:283–290
60. Corso A, Lorenzi A, Terulla V, et al. Modification of thrombomodulin plasma levels in refractory myeloma patients during treatment with thalidomide and dexamethasone. Ann Hematol 2004;83:588–591
61. Zangari M, Barlogie B, Thertulien R, et al. Thalidomide and deep vein thrombosis in multiple myeloma: risk factors and effect on survival. Clin Lymphoma 2003;4:32–35
62. Chen SJ, Zelent A, Tong JH, et al. Rearrangements of the retinoic acid receptor alpha and promyelocytic leukemia zinc finger genes resulting from t(11;17)(q23;q21) in a patient with acute promyelocytic leukemia. J Clin Invest 1993; 91:2260–2267
63. Licht JD, Shaknovich R, English MA, et al. Reduced and altered DNA-binding and transcriptional properties of the PLZF-retinoic acid receptor-alpha chimera generated in t(11;17)-associated acute promyelocytic leukemia. Oncogene 1996;12:323–336
64. Chen A, Licht JD, Wu Y, Hellinger N, Scher W, Waxman S. Retinoic acid is required for and potentiates differentiation of acute promyelocytic leukemia cells by non-retinoid agents. Blood 1994;84:2122–2129
65. Dong S, Tong JH, Huang W, et al. Molecular study on the chromosome 15 breakpoints in the translocation t(15; 17) in acute promyelocytic leukemia (APL). Sci China B 1993;36: 1101–1109
66. Dong S, Tong J, Wu Y, et al. Molecular study of the mechanism of chromosomal translocation (15;17) in acute promyelocytic leukemia (APL). Yi Chuan Xue Bao. 1993; 20:381–388
67. Geng JP, Tong JH, Dong S, et al. Localization of the chromosome 15 breakpoints and expression of multiple PML-RAR alpha transcripts in acute promyelocytic leukemia: a study of 28 Chinese patients. Leukemia 1993; 7:20–26
68. Wang ZY, Chen Z, Huang W, et al. Problems existing in differentiation therapy of acute promyelocytic leukemia (APL) with all-trans retinoic acid (ATRA). Blood Cells 1993;19:633–641 (discussion 642–637)
69. Schneider W, Runde V, Aul C. From fatal hemorrhagic diathesis to life-threatening thrombosis risk. New complications of a "gentle" treatment of acute promyelocytic

leukemias with all-trans-retinoic acid. Dtsch Med Wochenschr 1991;116:1971–1975
70. Runde V, Aul C, Heyll A, Schneider W. All-trans retinoic acid: not only a differentiating agent, but also an inducer of thromboembolic events in patients with M3 leukemia. Blood 1992;79:534–535
71. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans-retinoic acid in acute promyelocytic leukemia. N Engl J Med 1997;337:1021–1028
72. Tallman MS. Retinoic acid syndrome: a problem of the past? Leukemia 2002;16:160–161
73. Fenaux P, De Botton S. Retinoic acid syndrome. Recognition, prevention and management. Drug Saf 1998;18:273–279
74. Escudier SM, Kantarjian HM, Estey EH. Thrombosis in patients with acute promyelocytic leukemia treated with and without all-trans retinoic acid. Leuk Lymphoma 1996;20: 435–439
75. de Lacerda JF, do Carmo JA, Guerra ML, Geraldes J, de Lacerda JM. Multiple thrombosis in acute promyelocytic leukaemia after tretinoin. Lancet 1993;342:114–115
76. Goldschmidt N, Gural A, Ben Yehuda D. Extensive splenic infarction, deep vein thrombosis and pulmonary emboli complicating induction therapy with all-trans-retinoic acid (ATRA) for acute promyelocytic leukemia. Leuk Lymphoma 2003;44:1433–1437
77. Brown JE, Olujohungbe A, Chang J, et al. All-trans retinoic acid (ATRA) and tranexamic acid: a potentially fatal combination in acute promyelocytic leukaemia. Br J Haematol 2000;110:1010–1012
78. Hashimoto S, Koike T, Tatewaki W, et al. Fatal thromboembolism in acute promyelocytic leukemia during all-trans retinoic acid therapy combined with antifibrinolytic therapy for prophylaxis of hemorrhage. Leukemia 1994;8: 1113–1115
79. Kwaan HC, Wang J, Boggio LN. Abnormalities in hemostasis in acute promyelocytic leukemia. Hematol Oncol 2002;20:33–41
80. Falanga A, Marchetti M, Barbui T. All-trans-retinoic acid and bleeding/thrombosis. Pathophysiol Haemost Thromb 2003;33(suppl 1):19–21
81. Douer D, Tallman MS. Arsenic trioxide: new clinical experience with an old medication in hematologic malignancies. J Clin Oncol 2005;23:2396–2410
82. Soignet SL, Maslak P, Wang ZG, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. N Engl J Med 1998;339:1341–1348
83. Niu C, Yan H, Yu T, et al. Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. Blood 1999;94:3315–3324
84. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst 2006;98:708–714
85. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998;339:584–590
86. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071–2084
87. Singh AK, Szczech L, Tang K, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085–2098
88. Luksenburg H, Weir A, Wager R. FDA briefing document. Oncologic Drugs Advisory Committee. Safety concerns associated with Aranesp (darbepoetin alfa) Amgen, Inc and Procrit (epoetin alfa) Ortho Biotech, L.P., for the treatment of anemia associated with cancer chemotherapy. Available at: www.fda.gov/ohrms/dockets/ac/04/briefing/4037B2_04_FDA-Aranesp-Procrit.htm. Accessed December 6, 2006
89. Stohlawetz PJ, Dzirlo L, Hergovich N, et al. Effects of erythropoietin on platelet reactivity and thrombopoiesis in humans. Blood 2000;95:2983–2989
90. Terpos E, Mougiou A, Kouraklis A, et al. Prolonged administration of erythropoietin increases erythroid response rate in myelodysplastic syndromes: a phase II trial in 281 patients. Br J Haematol 2002;118:174–180
91. Raza A, Meyer P, Dutt D, et al. Thalidomide produces transfusion independence in long-standing refractory anemias of patients with myelodysplastic syndromes. Blood 2001;98:958–965
92. Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. J Clin Oncol 2002;20: 4083–4107
93. Barbui T, Finazzi G, Grassi A, Marchioli R. Thrombosis in cancer patients treated with hematopoietic growth factors–a meta-analysis. On behalf of the Subcommittee on Haemostasis and Malignancy of the Scientific and Standardization Committee of the ISTH. Thromb Haemost 1996;75:368–371
94. Grem JL, McAtee N, Murphy RF, et al. Phase I and pharmacokinetic study of recombinant human granulocyte-macrophage colony-stimulating factor given in combination with fluorouracil plus calcium leucovorin in metastatic gastrointestinal adenocarcinoma. J Clin Oncol 1994;12: 560–568
95. LeBlanc R, Roy J, Demers C, Vu L, Cantin G. A prospective study of G-CSF effects on hemostasis in allogeneic blood stem cell donors. Bone Marrow Transplant 1999;23:991–996
96. Falanga A, Marchetti M, Evangelista V, et al. Neutrophil activation and hemostatic changes in healthy donors receiving granulocyte colony-stimulating factor. Blood 1999;93:2506–2514
97. Topcuoglu P, Arat M, Dalva K, Ozcan M. Administration of granulocyte-colony-stimulating factor for allogeneic hematopoietic cell collection may induce the tissue factor-dependent pathway in healthy donors. Bone Marrow Transplant 2004;33:171–176
98. Gordon LI, Kwaan HC. Thrombotic microangiopathy manifesting as thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in the cancer patient. Semin Thromb Hemost 1999;25:217–221
99. Kwaan HC, Gordon LI. Thrombotic microangiopathy in the cancer patient. Acta Haematol 2001;106:52–56
100. Medina PJ, Sipols JM, George JN. Drug-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Curr Opin Hematol 2001;8:286–293
101. Ravandi-Kashani F, Cortes J, Talpaz M, Kantarjian HM. Thrombotic microangiopathy associated with interferon

therapy for patients with chronic myelogenous leukemia: coincidence or true side effect? Cancer 1999;85:2583–2588
102. Al-Zahrani H, Gupta V, Minden MD, Messner HA, Lipton JH. Vascular events associated with alpha interferon therapy. Leuk Lymphoma 2003;44:471–475
103. Humphreys BD, Sharman JP, Henderson JM, et al. Gemcitabine-associated thrombotic microangiopathy. Cancer 2004;100:2664–2670
104. Vesely SK, George JN, Lammle B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. Blood 2003;102:60–68
105. Zheng XL, Kaufman RM, Goodnough LT, Sadler JE. Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura. Blood 2004;103: 4043–4049
106. Veyradier A, Obert B, Houllier A, Meyer D, Girma JP. Specific von Willebrand factor-cleaving protease in thrombotic microangiopathies: a study of 111 cases. Blood 2001; 98:1765–1772
107. Fung MC, Storniolo AM, Nguyen B, Arning M, Brookfield W, Vigil J. A review of hemolytic uremic syndrome in patients treated with gemcitabine therapy. Cancer 1999;85: 2023–2032
108. Walter RB, Joerger M, Pestalozzi BC. Gemcitabine-associated hemolytic-uremic syndrome. Am J Kidney Dis 2002;40:E16
109. Al Aly Z, Philoctete Ashley JM, Gellens ME, Gonzalez EA. Thrombotic thrombocytopenic purpura in a patient treated with imatinib mesylate: true association or mere coincidence? Am J Kidney Dis 2005;45:762–768
110. George JN, Li X, McMinn JR, Terrell DR, Vesely SK, Selby GB. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome following allogeneic HPC transplantation: a diagnostic dilemma. Transfusion. 2004;44: 294–304
111. Iacopino P, Pucci G, Arcese W, et al. Severe thrombotic microangiopathy: an infrequent complication of bone marrow transplantation. Gruppo Italiano Trapianto Midollo Osseo (GITMO). Bone Marrow Transplant 1999;24:47–51
112. Elliott MA, Nichols WL Jr, Plumhoff EA, et al. Posttransplantation thrombotic thrombocytopenic purpura: a single-center experience and a contemporary review. Mayo Clin Proc 2003;78:421–430
113. Wiener Y, Nakhleh RE, Lee MW, et al. Prognostic factors and early resumption of cyclosporin A in renal allograft recipients with thrombotic microangiopathy and hemolytic uremic syndrome. Clin Transplant 1997;11:157–162
114. McCauley J, Bronsther O, Fung J, Todo S, Starzl TE. Treatment of cyclosporin-induced haemolytic uraemic syndrome with FK506. Lancet 1989;2:1516