

Coagulation Conundrums in Malignant Hematology

By James M. Coghill, MD, and Alice Ma, MD

The hypercoagulable state associated with solid tumors and the hemorrhagic tendency of thrombocytopenic patients with hematologic malignancies are both widely realized. Perhaps less appreciated, however, are the thromboembolic complications and novel coagulopathic mechanisms that can develop in patients with myelo- and lympho-proliferative disorders, plasma cell dyscrasias, certain subtypes of acute leukemia, and in the hematopoietic stem cell transplantation (HSCT) setting. Such patients are at risk for a wide spectrum of disorders including acquired von Willebrand disease (vWD), disseminated intravascular coagulation (DIC), the development of inhibitors to various coagulation factors, thrombotic thrombocytopenic purpura (TTP), and hepatic veno-occlusive disease (VOD). The practicing hematologist must therefore be well versed in the appropriate management of difficult patients who may simultaneously present with risk factors for both bleeding and thrombosis.

This year's Education Session titled "Thrombosis and Bleeding Complications in Malignant Hematologic Disorders," which took place yesterday and is scheduled again today at 7:30 a.m., included several excellent presentations on the diagnosis and management of thromboembolic and hemorrhagic disorders in this unique patient population. Dr. Charles Eby began the program with an overview of the bleeding complications that can occasionally be seen in patients with plasma cell dyscrasias. He discussed how abnormal paraprotein production can result in platelet dysfunction, acquired vWD, neutralization of coagulation factors, fibrin polymerization defects, and direct damage to the walls of small blood vessels. He went on to discuss mechanisms for the high incidence of venous thromboembolism (VTE) observed in multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS) including the generation of prothrombotic IL-6, the stabilization of fibrin polymers by paraproteins leading to resistance to fibrinolysis, the generation of inhibitors to protein S, and iatrogenic causes such as thalidomide and lenalidomide. Dr. Eby concluded by presenting therapeutic approaches that can be utilized by practicing hematologists for the prevention of VTE including the prophylactic use of low molecular weight heparin (LMWH) and aspirin.

Dr. Hau Kwaan continued the program with a thorough discussion of common coagulation abnormalities occurring in the setting of acute leukemia. Emphasis was directed at the hypercoagulable state that can occur in these patients, something that may be overlooked given their propensity to bleed from disease and therapy-related thrombocytopenia. Mechanisms accounting for this increased susceptibility to thrombosis include the generation of tissue factor by leukemia cells themselves (particularly in the M3 AML subtype); increased blood viscosity from hyperleukocytosis; acquired activated protein C (APC) resistance; and various iatrogenic causes including indwelling central venous access devices and chemotherapeutic agents such as L-asparaginase and glucocorticoids. Dr. Kwaan concluded with a discussion of several bleeding complications that can develop in patients with acute leukemia including DIC, the development of factor VIII inhibitors, and enhanced fibrinolysis resulting from augmented tissue plasminogen activator (tPA) production and increased plasmin generation by annexin II.

Dr. Frederick Rickles concluded the program by reviewing strategies for the prevention and treatment of thromboembolic complications in those with hematologic malignancies. He pointed out that, in contrast to patients with solid tumors, there is a paucity of prospective data addressing thromboprophylaxis and therapeutic anticoagulation for the hematologic malignancy population, and emphasized the need for future randomized clinical trials. Nevertheless, Dr. Rickles outlined several reasonable anticoagulation approaches that can be used for VTE prevention and treatment. LMWH dosing strategies for patients with co-existing thrombocytopenia, the management of catheter-related thrombosis, and the role of removable inferior vena-cava filters were all discussed.

For those wishing to learn more, check out the oral presentation by Dr. Antonio Palumbo et al. (abstract #310) scheduled for the "Antithrombotic Therapy: New Anticoagulants" session on Monday at 11:00 a.m., which will provide an overview of a phase III randomized controlled trial comparing enoxaparin, warfarin, and aspirin for the prevention of thromboembolic complications in myeloma patients receiving thalidomide-containing regimens. Several posters may also be of interest, including works by Polizzotto et al. (abstract #1872) focusing on anticoagulation in thrombocytopenic patients receiving chemotherapy and Muslimani et al. (abstract #1878) specifically looking at anticoagulation in those with lymphoma.