Lecture
Risk Assessment and Treatment of Bleeding in Cancer Patients

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Hemostatic Complications of Hematopoietic Stem Cell Transplantation: From Hemorrhage to Microangiopathies and VOD

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Patients who undergo hematopoietic stem cell transplantation (SCT) have unique toxicities and correspondingly specialized requirements in supportive care given the intensity of cytotoxic therapy to which they are exposed, the severe immuno-suppression they undergo, their temporary inability to produce blood cells, and the fact that their blood type may change as they become a temporary or permanent chimera in the allogeneic setting.

Hemorrhagic complications in SCT most commonly occur in the context of thrombocytopenia. Platelets are transfused either to prevent bleeding or to treat active bleeding. It has become common practice for physicians to use platelet transfusions to prevent serious bleeding when the platelet count is less than 20,000/μL [1]. However, more recent data has shown that serious bleeding usually occurs only when the platelet count is below 10,000/μL and fatal bleeding is unlikely to occur at platelet counts above 5,000/μL. Various studies have shown that the threshold for prophylactic platelet transfusion should be 10,000/μL or less and thus a National Institute of Health (NIH) consensus conference recommended that the 20,000/μL value threshold traditionally used for prophylactic platelet transfusion could be safely lowered for many patients. Currently, many physicians and hospital guidelines use platelet counts of 10,000 or 5,000/μL as the indication for transfusion for uncomplicated patients. However, many SCT recipients are febrile and often have intercurrent lesions such as mucositis, and thus many of these patients are transfused at platelet counts of 20,000/μL or higher. In actively bleeding patients, platelet transfusions should be considered in those with a platelet count of less than approximately 75,000/μL and an attempt to achieve a level of above 50,000/μL is usually recommended. In special situations where patients' platelets may be dysfunctional due to drugs (e.g. cyclophosphamide) or uremia, the bleeding time may be much longer than would be expected based on the degree of thrombocytopenia and in such situations the decision to give a platelet transfusion can be made on clinical grounds alone.

There is a dose response effect from platelet transfusion such that within one hour after transfusion the platelet count increases approximately 10,000/μL when 1×10^{11} platelets are transfused into an average (70 kg) patient. Typically, one platelet concentrate per 10 kg of body weight is administered to increase the platelet count by approximately 40,000/μL and a one-hour post transfusion platelet count is useful as an excellent predictor of an effective platelet transfusion, with the corrected count increment as a common calculation used to determine refractoriness. It now seems clear that ABO incompatible platelet transfusions are associated with reduced post transfusional platelet recovery [2, 3]. Thus the use of ABO matched platelets that are approximately 24 h in storage can be tried to produce a satisfactory increment, and if these are unsuccessful, efforts should then be made to use platelets that are an HLA-match

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to the recipient [2]. In cases where the patient is refractory despite HLA matched product, case reports have described the beneficial effect of intravenous immunoglobulin (IVIG) in improving the response to platelet transfusion in allo-immunized, refractory patients, although one large prospective study found no significant benefit from IVIG use [4, 5]. One of the best strategies for the prevention of allo-immunizational platelet refractoriness is the use of a leukocyte depletion, which has been shown in a series of clinical trials to reduce the incidence of allo-immunization, and delay the onset of refractoriness [6]. This approach also appears to decrease the incidence of platelet transfusion reactions, which are primarily related to cytokine release (including IL-1 and IL-6) from degenerating leukocytes [7]. Clinical trials in SCT of platelet growth factors thrombopoietin (TPO) and PEG megakaryocyte growth and development factor (MGDF) have not fulfilled their initial promise and their role remains investigational at this time [8].

Bleeding due to coagulation factor deficiencies are relatively uncommon during SCT, although the use of broad spectrum antibiotics, and decreased nutritional intake can contribute to vitamin K dependent factor deficiencies that are readily correctable with appropriate supplementation of vitamin K. Fresh frozen plasma (FFP) is indicated for documented coagulation factor deficiencies and multiple factor deficiencies in selected patients [9, 10]. Disseminated intravascular coagulation can occur in SCT as a result of multiple underlying issues, including sepsis. Treatment of the underlying cause of the DIC is essential since without treatment transfusion of blood components merely adds more substrate for the coagulation process. Mild forms of DIC usually do not require aggressive transfusional support, but in the more extreme forms there is usually significant deficiency of factors V, VIII, fibrinogen and platelets [10]. The replacement of coagulation factors in the management DIC should be based on laboratory abnormalities and not on arbitrary formulas, and when replacement is necessary FFP is usually used to replace all factors. Cryoprecipitate contains factor VIII, fibrinogen and vWF. It is thus primarily used as a means of restoring fibrinogen levels in the SCT population, but it is not a suitable source of coagulation factors II, V, VII, IX, X, XI or XII [10]. Factor VII concentrates have recently become available and are especially helpful in bleeding complications of SCT, including VOD where isolated factor VII deficiencies occur and large volume FFP infusions can be hazardous with the risk of exacerbating fluid overload. As mentioned previously, mucosal damage from chemotherapy and irradiation can predispose to bleeding. Hemorrhagic cystitis is a special situation in which acrolein-mediated injury from cyclophosphamide exposure causes profound epithelial disruption in the bladder. Prophylaxis with saline diuresis and mesna are effective with treatment of established bleeding centered on the use of bladder irrigation and correcting any bleeding diathesis with appropriate blood products and factor VII concentrates.

The vascular endothelium is a key platform in hemostasis; it is repeatedly exposed to toxic agents both during the preparation for SCT and for the first 6 to 12 months following SCT. Toxins range from cytotoxic chemotherapy (including cyclophosphamide; nitrosureas, and platinum-based compounds), radiation, lipo-polysaccharide-mediated injury from bacterial endotoxins, fungi or cytomegalovirus, numerous cytokines, and drugs including cyclosporin [11, 12]. Moreover, the allogeneic stimulus of donor immunity is also contributory, and opportunistic infections with bartonella-like inclusions in erythrocytes have been reported as associated with thrombotic microangiopathy after SCT. In aggregate, these multiple exposures cause partial obstruction in small arterioles and capillaries with microthrombi consisting of activated platelet clumps and overlying proliferation of endothelial cells [11]. This impaired blood flow produces a spectrum of clinical syndromes ranging from clinically insignificant (mechanical) hemolysis evidenced by red cell fragmentation and a mild increase in LDH to the full pentad of thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (TTP/HUS): characterized by anemia, thrombocytopenia, fever, uremia and neurologic dysfunction [13]. Therapy centers on plasma exchange [14]. Additional interventions over and above this have so far been unrewarding, although recent reports of defibrotide use for this complication with apparent success are of interest [15].

Diffuse alveolar hemorrhage has been associated with microangiopathy after allo-SCT and is a significant clinical problem during SCT [16]. The syndrome is steroid responsive, with factor VII concentrates showing utility in the management of frank pulmonary bleeding when used in conjunction with solumedrol.

Microangiopathic injury during SCT also extends to the clinical syndrome of hepatic veno-occlusive disease (VOD). This is characterized by liver enlargement, pain, fluid retention, weight gain and jaundice [17]. Its onset is typically by day plus 30 after SCT although later onset has been described. The incidence ranges from 10 to 60% and is influenced by differences in conditioning regimens and patient characteristics. Prognosis is also variable. Mild disease is defined by no apparent adverse effect from liver dysfunction with complete resolution of symptoms and signs.

Moderate disease is characterized by adverse effects of liver dysfunction requiring therapies such as dieresis for fluid retention and analgesia for RUQ pain but with eventual complete resolution. The majority of patients fall into the mild to moderate category. However, a significant fraction of patients develop severe VOD, in which most patients are incurable with an all-cause fatality rate approaching 100% by day plus 100 post-SCT [17, 18]. Multi-organ failure is characteristic of this group [17, 18]. There is a growing body of evidence indicating that early injury to vascular endothelium and sinusoidal endothelium either directly by the conditioning regimen or through the production of cytokines are important initiating events [19–23]. An important new risk factor for VOD has been the use of Mylotarg for the treatment of AML. This anti CD-33 monoclonal antibody therapy results in significant sinusoidal endothelial damage in a subset of patients with intense fibrosis, sinusoidal obstruction and severe VOD occurring both with the use of the agent alone, after SCT and pre-SCT. Other major risk factors for VOD include high dose regimens incorporating cyclophosphamide and busulfan, pre-existing liver damage, and allogeneic SCT, especially with increasing histo-incompatibility between donor and recipient [24]. Treatment targeting endothelial cell injury with the use of fibrinolytic and anti-coagulant therapy has been a major focus to date, but the use of t-PA with or without heparin has been limited by a high incidence of severe and fatal bleeding [25]. Derived strategies modulating endothelial cell injury without significant systemic bleeding have led to the development of defibrotide for this indication with both pre-clinical and clinical studies supporting its use in this setting [26–29]. Prospective, multi-institutional trials of defibrotide in the treatment of severe VOD are now underway in the United States and Europe. Other approaches targeting hepatocellular injury with anti-oxidant support, such as N-acetyl cysteine, are also under study and suggest a possible platform for a combination approach with promising agents such as defibrotide, both as therapy and as prophylaxis [29, 30].

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