Noninfectious Acute Lung Injury Syndromes Early After Hematopoietic Stem Cell Transplantation

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KEYWORDS

• Hematopoietic stem cell transplantation • Idiopathic pneumonia syndrome (IPS)
• Diffuse alveolar hemorrhage (DAH) • Peri-engraftment respiratory distress syndrome (PERDS)

KEY POINTS

- Acute lung injury remains a major cause of early post–hematopoietic stem cell transplantation (HSCT) nonrelapse mortality.
- Pulmonary function testing results before transplant may help to identify a group of patients at high risk for post-HSCT respiratory failure and death.
- Early enthusiasm for treatment of idiopathic pneumonia syndrome with etanercept has been dampened by results of recent studies in adult HSCT recipients.

INTRODUCTION

Hematopoietic (blood and marrow) stem cell transplantation (HSCT) is an important, potentially curative treatment option for patients with benign and malignant hematologic diseases. Over the past decade, the number of HSCT procedures performed in the United States has steadily increased, with more than 8000 allogeneic procedures and almost 14,000 autologous procedures reported in 2015.[1] In the past, conditioning regimen–related toxicity greatly limited the applicability of allogeneic transplantation to only younger patients without major comorbidities. However, the development of reduced-intensity conditioning (RIC) and nonmyeloablative regimens that rely primarily on immunologic mechanisms (graft vs leukemia) rather than myeloablation to eradicate malignancy has greatly reduced early toxicity and allowed transplantation of older and sicker patients.[1–4]

Pulmonary complications, both infectious and noninfectious, occur in 20% to 60% of HSCT recipients, although rates and severity may differ based on the intensity and type of conditioning regimen, timing of immune system reconstitution, procedure indication, type of transplant (autologous vs allogeneic), presence of preexisting lung disease, and era of transplantation, with more recent studies reporting lower rates of respiratory failure.[5–11] Post-HSCT complications have traditionally been categorized into 3 periods defined by distinct phases after the procedure, as certain complications are more likely to occur with certain periods.[9] These phases include the following:

- Phase 1: Preengraftment (neutropenic) phase (1–4 weeks posttransplant)
- Phase 2: Early postengraftment phase (engraftment to day 100)
- Phase 3: Late phase (beyond day 100)

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Despite advances in diagnosis and treatment with potent antimicrobial agents for prophylaxis, pneumonia remains a major cause of death after HSCT. These infectious complications are reviewed in detail in other articles in this issue. The focus of this article is on early (phases 1 and 2) noninfectious pulmonary complications after HSCT.

NONINFECTIOUS ACUTE LUNG INJURY: PREENGRAFTMENT AND EARLY PHASES

Noninfectious pulmonary complications are important causes of early death and morbidity after HSCT. These complications include pulmonary edema, transfusion-related acute lung injury (TRALI), and several severe acute lung injury syndromes that together fall under the umbrella term idiopathic pneumonia syndrome (IPS). Drug-induced pneumonitis, cryptogenic organizing pneumonia, and acute fibrinous organizing pneumonia are conditions that may be seen in early or later time periods after HSCT. They are briefly discussed in this section.

Pulmonary Edema

Pulmonary edema may be seen in the first few weeks after either autologous or allogeneic transplantation. Large volumes of fluid are frequently administered concurrently with conditioning regimen chemotherapy to reduce toxicity. Transfusion of blood products, infusion of intravenous medications, and parenteral nutrition are other common reasons for volume administration in the early posttransplant period. Hypoalbuminemia and subsequent development of chemotherapy-induced cardiac dysfunction and/or renal failure further increases the propensity for developing hydrostatic pulmonary edema. Rapid infusion of multiple units of blood products increases the risk of transfusion-associated circulatory overload, especially in older patients with cardiac and/or renal dysfunction.[12] Lung injury from chemotherapy and radiation, blood transfusions, and sepsis may increase capillary permeability and also contribute to pulmonary edema risk. Important clinical findings include weight gain, rapid onset of dyspnea, bibasilar rales on auscultation, hypoxemia, and radiographic findings consistent with pulmonary edema.[13] On high-resolution computerized tomography (CT) chest scan, characteristic findings include interlobular septal thickening and bilateral ground glass opacities; pleural effusions also may be seen.[14] Close attention to volume status and judicious use of diuretics may reduce the risk of pulmonary edema development.[15]

Transfusion-Related Lung Injury

TRALI may occur after HSCT and can develop concurrently with other types of lung injury.[16,17] It typically manifests within 6 hours of blood product transfusion. Plasma-rich products such as platelets, cryoprecipitate, and fresh frozen plasma confer the greatest risk. Notably, there have been 2 case reports of TRALI developing immediately after infusion of the bone marrow graft.[18,19] Patients develop acute onset of dyspnea and often have fever and hypotension. Acute leukopenia and thrombocytopenia may be seen, but this is not a distinguishing feature in patients in the preengraftment phase. Chest radiograph (CXR) findings are similar to patients with other types of pulmonary edema. Cardiac imaging typically shows normal left ventricular function. Mechanism of injury has not been fully elucidated, but involves a 2-step process initiated by trafficking of primed neutrophils to damaged lung microvasculature and subsequent neutrophil activation by antibodies in transfused blood products directed against human leukocyte antigen (HLA) and human neutrophil antigens. Neutrophils also may be activated by other substances in transfused blood, such as bioactive lipids and soluble CD40 ligand.[20] The activated neutrophils release proinflammatory cytokines, reactive oxygen species, and proteases that damage the lung. Reports of TRALI in neutropenic patients support the hypothesis that passively transfused HLA antibodies also may directly target antigens on pulmonary vascular endothelium.[20–22] The HSCT recipient may be at especially high risk for TRALI, as transfusions are frequently required and many of these patients have underlying systemic inflammation triggered by condition regimen toxicity, sepsis, and graft versus host disease (GVHD).[17]

Treatment is supportive, as no specific intervention reliably hastens recovery. TRALI results in respiratory failure requiring mechanical ventilation in most patients.[20] In the nontransplant setting, mortality rates ranging from 5% to more than 40% have been reported.[21,23] Use of a restrictive transfusion policy appears to reduce risk.[20] Notably, TRALI rates have declined in the United States over the past decade as blood banks have adopted “TRALI mitigation policies,” such as transfusing plasma from donors with low risk for transmitting alloantibodies (male and nulliparous female individuals).[24]

IDIOPATHIC PNEUMONIA SYNDROME

Diffuse pneumonitis is a devastating early complication after HSCT. As no infectious etiology is