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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

identified in up to half of these cases, the term "idiopathic pneumonia syndrome (IPS)" was coined to describe this heterogeneous group of noninfectious acute lung injury disorders.[5,25] Notably, IPS includes a subset of conditions, such as diffuse alveolar hemorrhage (DAH) and peri-engraftment respiratory distress syndrome (PERDS), that share clinical features and risk factors but have distinct clinical presentations and treatment approaches. These conditions are discussed separately.

Patients with IPS develop acute onset of cough, dyspnea with or without fever, hypoxemia, and diffuse infiltrates on CXR that often progresses quickly to respiratory failure.[5,26] Bronchoscopy with bronchoalveolar lavage (BAL) to assess for infectious processes is recommended, as quantitative polymerase chain reaction assays have greatly expanded our capability of diagnosing occult respiratory infections. A recent study indicated that almost 57% of patients previously given the diagnosis of IPS were, in fact, found to have a detectable pathogen on BAL. These pathogens were predominantly respiratory viruses (eg, human herpes virus-6, human rhinovirus, cytomegalovirus) or *Aspergillus* species.[27] Although treatment options for many of these infections remain limited, ruling out an underlying infection would be important before considering treatment with immunomodulatory therapies (discussed later in this article). Pathologic findings of IPS are similar to what has been described in patients with the acute respiratory distress syndrome (ARDS), with diffuse alveolar damage and interstitial pneumonitis as the most commonly described findings.[25,28]

IPS may occur in 2% to 10% of HSCT recipients and has a mortality rate exceeding 60% in most studies.[29–34] In 2011, the American Thoracic Society (ATS) proposed an updated definition of IPS that included clinical, physiologic, and radiographic findings consistent with diffuse acute lung injury but specifically excluded respiratory dysfunction due to cardiac, renal, or iatrogenic volume overload[35] (**Box 1**). IPS typically occurs in the first 4 months after HSCT, with most cases developing in the preengraftment or early postengraftment phase. Recent studies have reported variable time of onset ranging from a median of 12 days to as long as 76 days after transplantation.[26,30–32]

Risk factors for the development of IPS include older age, use of a high-dose conditioning regimen that includes total body irradiation (TBI), presence of high-grade acute GVHD in allogeneic recipients, and physiologic evidence of lung disease before transplantation.[34–39] Because both autologous and allogeneic HSCT recipients can develop IPS, conditioning regimen–related toxicity is thought to have a central role in inflicting lung injury.[33,34,40] In support of this concept is the finding that allogeneic HSCT recipients who have received RIC regimens have lower rates of IPS. In a study from the Fred Hutchinson Cancer Research Center (FHCRC), 917 conventional transplant recipients were compared with 183 recipients who had received nonmyeloablative conditioning.[39] Even though the nonmyeloablative cohort was older, rates of IPS were significantly lower than observed in the conventional group (2.2% vs 8.4%). Older patients (age >40) who received a myeloablative-conditioning regimen that included high-dose TBI appeared to be at especially high risk for IPS (16.5%). Notably, in both the nonmyeloablative and conventional conditioning regimen groups, the presence of severe GVHD conferred increased risk for IPS, highlighting the importance of the alloimmune response in amplifying lung injury. In this study, although the nonmyeloablative conditioning regimen group had lower rates of IPS, its clinical manifestation was not less severe when it occurred; respiratory failure developed in most patients and mortality exceeded 75%.[39]

Pathophysiology

Although the pathophysiology of IPS remains incompletely understood, preclinical and translational studies have greatly informed our knowledge of mechanisms of lung injury and have served as the foundation for clinical trials investigating therapeutic approaches. These studies were reviewed in a recent official ATS Research Statement on IPS.[35] Murine models of allogeneic HSCT demonstrate extensive inflammation/injury in alveolar, interstitial, bronchial, and vascular tissues. In particular, animal data suggest that pulmonary endothelial cell damage caused directly by conditioning regimen toxicity and indirectly through activation of a robust inflammatory response are the principal events in the development of IPS.[41] The cytokine tumor necrosis factor–alpha (TNF-α) appears to be a key mediator of this inflammatory response. Murine studies have shown that increasing levels of donor-derived TNF-α in BAL fluid and lung tissue are associated with IPS severity and that transplantation of stem cells from TNF-α knockout mice or administration of a neutralizing TNF-binding antibody greatly reduced lung injury.[42,43] In addition to TNF-α, high levels of lipopolysaccharide (LPS) or endotoxin also have been observed in the BAL fluid of mice. LPS is a component of the cell membrane of gram-negative bacteria and is capable of

Box 1
Definition of idiopathic pneumonia syndrome

I. Evidence of widespread alveolar injury:
   a. Multilobar infiltrates on routine chest radiographs or computed tomography
   b. Symptoms and signs of pneumonia (cough, dyspnea, tachypnea, rales)
   c. Evidence of abnormal pulmonary physiology
      1. Increased alveolar to arterial oxygen difference
      2. New or increased restrictive pulmonary function test abnormality

II. Absence of active lower respiratory tract infection based on the following:
   a. Bronchoalveolar lavage negative for significant bacterial pathogens, including acid-fast bacilli, *Nocardia,* and *Legionella* species
   b. Bronchoalveolar lavage negative for pathogenic nonbacterial microorganisms:
      1. Routine culture for viruses and fungi
      2. Shell vial culture for CMV and RSV
      3. Cytology for CMV inclusions, fungi, and *Pneumocystis jiroveci (carinii)*
      4. Direct fluorescence staining with antibodies against CMV, RSV, HSV, VZV, influenza virus, parainfluenza virus, adenovirus, and other organisms
   c. Other organisms/tests to also consider:
      1. Polymerase chain reaction for human metapneumovirus, rhinovirus, corona virus, and HHV6
      2. Polymerase chain reaction for *Chlamydia, Mycoplasma,* and *Aspergillus* species
      3. Serum galactomannan ELISA for *Aspergillus* species
   d. Transbronchial biopsy if condition of the patient permits

III. Absence of cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as etiology for pulmonary dysfunction

Abbreviations: CMV, cytomegalovirus; ELISA, enzyme-linked immunosorbent assay; HHV6, human herpes virus 6; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

Reprinted from Panoskaltsis-Mortari A, Griese M, Madtes DK, et al, on behalf of the American Thoracic Society Committee on Idiopathic Pneumonia Syndrome. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. Am J Respir Crit Care Med 2011;183:1263; with permission of the American Thoracic Society.

directly activating the innate immune system. Macrophages and other immune cells produce TNF-α in response to LPS stimulation. In murine models of IPS, LPS injection has been shown to markedly increase lung injury.[43] It has been hypothesized that conditioning regimen–related injury or acute GVHD of the gastrointestinal tract facilitates bacterial translocation and subsequent release of LPS into the systemic and ultimately pulmonary circulation, resulting in production of high levels of proinflammatory cytokines, including TNF-α.[35] Animal models indicate that blocking the effects of TNF-α does not completely prevent IPS and numerous other mechanisms of lung injury are thought to play an important role.[35] Nevertheless, the preclinical data provided a compelling rationale to investigate blockade of the TNF-α pathway in human clinical trials of IPS.

Treatment

Treatment of IPS with high or intermediate doses of corticosteroids is generally ineffective, with a possible exception for patients with DAH.[34] After single-center, nonrandomized studies suggested reduction in short-term mortality after administration of the soluble TNF-receptor etanercept, a randomized, double-blind placebo-controlled trial of etanercept (0.4 mg/kg twice weekly for a total of 8 doses) and methylprednisolone (2 mg/kg per day) versus methylprednisolone alone for the treatment of IPS was undertaken.[30,32,44] Clinical response to treatment was defined by survival to study day 28 and discontinuation of supplemental oxygen for at least 72 hours by day 28. A sample size of 120 patients was targeted. Unfortunately, patient accrual was slow and the study was halted

after enrollment of only 34 patients. Although the study was underpowered and definitive conclusions could not be made, no difference in clinical response was seen. Ten (63%) of 18 patients in the etanercept arm achieved clinical response, whereas 12 (67%) of 18 in the placebo arm met criteria for response. There was also no difference in outcome at day 56. Overall survival at 1 year remained similarly poor in both groups, with 77% mortality in the treatment arm and 83% in the placebo group. This study proved to be very challenging to conduct. Almost 40% of patients in the etanercept arm received only 2 or fewer doses. As an explanation for early discontinuation of study drug, investigators reported hesitance to continue "blinded" treatment, especially if the patient did not demonstrate early clinical improvement.[30] The investigators also commented on improved short-term outcomes in both study groups compared with prior and speculated whether the clinical characteristics of IPS had changed over the past decade. In fact, in this study, more than 40% of patients had received RIC; it is possible that less toxicity from chemoradiation resulted in lower levels of TNF-α and diminished likelihood of response to etanercept treatment. In support of this hypothesis is the result of a recent multicenter, albeit, nonrandomized phase II study of etanercept treatment in pediatric patients with IPS demonstrating significant short-term and long-term benefit with 28-day and 1-year survival rates of 89% and 63%, respectively.[45] In contrast to the adult study, in this pediatric trial, only 4% of the patients received RIC regimens. In the future, a more tailored (eg, patients with high levels of TNF-α or HSCT recipients who receive conventional conditioning regimens) approach to treating patients with IPS could be considered, but this strategy would need to be evaluated in clinical trials.[30] Despite the results of this one randomized study in adults, in the absence of other treatment options, etanercept remains a therapeutic option for patients with severe IPS.

Supportive treatment for very severe ARDS with extracorporeal life support (ECLS) has increasingly become incorporated into clinical practice.[46] Major ECLS-related complications include sepsis and hemorrhage. For this reason, immunosuppressed, thrombocytopenic HSCT recipients are generally not considered candidates for this type of support. Advances in ECLS technology, however, have reduced complications and permitted use of lower levels, or even withholding, of systemic anticoagulation.[47] With these advances, there have been case reports of patients with IPS who were successfully bridged to recovery with ECLS even while receiving treatment with corticosteroids and etanercept.[48,49] Nevertheless, as outcomes of patients with IPS remain generally poor for adult patients, the risk of a "bridge to nowhere" scenario is not insignificant and can result in extremely difficult situations in which a potentially alert but critically ill patient remains dependent on ECLS.[50] Thus, it is essential that before ECLS technologies are used that clear expectations are established with the patient and family regarding the high likelihood of treatment failure, anticipated complications, duration and limits of extracorporeal support, and the factors the medical team will use to recommend withdrawal of ECLS. Early consultation with a palliative care team, if available, may be helpful.[50]

DIFFUSE ALVEOLAR HEMORRHAGE

DAH is a form of IPS with a distinct clinical presentation characterized by the development of dyspnea, fever, multifocal infiltrates on CXR, and rapid progression to respiratory failure. Hemoptysis may occur but is not always seen. Typical findings on high-resolution CT scan includes diffuse ground glass opacities in the mid and lower lung zones more prominent in the perihilar regions with or without interlobular septal thickening, resulting in a "crazy-paving" appearance.[51] It is distinguished from other types of IPS by bronchoscopy, during which the finding of progressively bloody return of BAL fluid from sequential aliquots in multiple lung segments is diagnostic if infectious etiologies and cardiogenic edema are excluded. The presence of more than 20% hemosiderin-laden macrophages on cytologic evaluation of BAL fluid also supports this diagnosis.[5,52] BAL fluid analysis, however, when compared with postmortem studies, appears to have suboptimal sensitivity and specificity for the diagnosis of DAH.[53] These studies have also shown that diffuse alveolar damage is a common concurrent finding.[53] Similar to other types of IPS, DAH is seen after both autologous and allogeneic transplantation. Recent studies report an incidence of 2% to 6%.[33,54–57] Although DAH and other types of IPS have overlapping risk factors, such as older age, severity of acute GVHD in allogeneic recipients, and intensity of the conditioning regimen (especially high-dose TBI or cyclophosphamide), treatment with RIC regimens has not been reported to lower incidence.[58] Although thrombocytopenia is almost universally present in all patients early after transplantation, it does not appear to be more common in patients who develop DAH.[59]

Outcomes

Although DAH typically occurs in the pre/peri-engraftment time frame, later onset has been reported in up to 42% of cases. Outcomes have been reported to be poor, with earlier publications showing mortality rates between 80% and 100%. More recent studies, however, suggest that survival may be improving. In a study of 223 consecutive HSCT recipients who underwent bronchoscopy between January 2002 and December 2004 at the University of Texas, MD Anderson Cancer Center, 53 patients were identified to have noninfectious DAH. One-month survival was 59% and 6-month survival was 46%, better than what had been reported in many previous studies.[52] Type of transplant and timing also may impact outcomes. In a large retrospective series from the Mayo Clinic of 1215 patients who underwent HSCT from October 1994 through June 2002, 48 patients (3.9%) were diagnosed with DAH. The development of DAH after autologous transplantation and early onset (within 30 days of transplant) had a significantly better outcome (approximately 70% survival) than DAH after allogeneic transplantation and onset beyond 30 days (approximately 30% survival).[60]

Treatment

Treatment of DAH has generally involved the administration of high doses of corticosteroids at varying doses (30 mg methylprednisolone per day to 1500 mg/d for a few days with subsequent tapering of dose) after several retrospective analyses reported improved outcomes.[61–63] More contemporary studies, however, have not confirmed this benefit.[56] In a recent single-center report of 119 consecutive HSCT recipients (predominantly allogeneic) admitted to the intensive care unit for treatment of DAH after HSCT, overall mortality was 85% at day 100. Notably, patients who initially received lower doses of corticosteroids (<250 mg/d methylprednisolone) had reduced intensive care unit and hospital mortality compared with patients who had received higher doses. However, as this was not a randomized study, significant bias in treatment decisions related to underlying severity of illness cannot be excluded; thus the validity of this finding is uncertain. Adjunctive treatment with the antifibrinolytic drug aminocaproic acid in a subset of these patients did not seem to impact outcome.[57] Unfortunately, there are no randomized, placebo-controlled trials evaluating the therapeutic effect of corticosteroids at varying doses for the treatment of post-HSCT DAH. Conduct of this type of trial would require clinical equipoise that likely does not exist in practice. Nevertheless, results of recent retrospective studies should caution providers against using high doses of corticosteroids.

The limited available treatment options for DAH have led to consideration of alternative approaches. Small retrospective series of patients with DAH have explored the use of intravenous treatment with the procoagulant agent recombinant Factor VIIa (rFVIIa) in conjunction with corticosteroids. These reports, however, have not suggested clinical benefit or improved outcomes, and treated patients appear to be at increased risk for thrombotic events.[55,64] In a recent Cochrane review, the investigators recommended against the off-label (eg, uncontrolled bleeding in patients without hemophilia) use of rFVIIa due to significant risk for thromboembolic events.[65] Recently, investigators have explored direct intrapulmonary instillation of rFVIIa to reduce risk of systemic thrombosis and to facilitate more direct exposure of the drug to sites of lung injury.[66] Although case reports and small series have suggested a possible benefit, this treatment approach cannot be endorsed without more evidence.[67–69]

PERI-ENGRAFTMENT RESPIRATORY DISTRESS SYNDROME

PERDS describes a form of acute lung injury that occurs around the time of engraftment (typically within 5 days) and is the pulmonary manifestation of a diffuse systemic capillary leak disorder termed the engraftment syndrome (ES). Although PERDS is categorized as a subset of IPS, it has a distinct clinical presentation and better prognosis. ES was initially described after syngeneic and autologous HSCT, but is also seen after conventional and RIC allogeneic transplantation.[70,71] In its fulminant presentation, patients with ES may have fever in the absence of infection, erythrodermatous rash, diarrhea, dyspnea, rapid weight gain from fluid retention, hepatic and renal dysfunction, hypotension, and, rarely, hemodynamic collapse.[70,72,73] There have been widely disparate incidence rates for ES reported in the literature due in part to varying clinical definitions and patient populations.[73,74] For example, patients undergoing transplantation for the POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome appear to be at especially high risk for ES (~50%).[75] In a study of a heterogeneous group of 1243 autologous HSCT recipients, PERDS was reported in 2.5%.[33] In the allogeneic setting, it may be difficult to distinguish ES from acute GVHD, as there is significant overlap in clinical symptoms.[73]

Risk factors for ES have not been clearly identified. Although some studies have reported female gender, rate of immune system reconstitution, peripheral blood versus bone marrow source of stem cells for transplantation, dose of CD34+ cells or mononuclear cells in the stem cell graft, type and intensity of pretreatment with chemotherapy (less treatment was associated with increased risk), and use of granulocyte macrophage colony-stimulating factor rather than granulocyte colony-stimulating factor as important risk factors, they have not been confirmed.[70,74,76–78] ES generally occurs in the setting of acute systemic inflammation with patients reported to have significantly elevated levels of several proinflammatory cytokines.[73,79,80]

Outcomes/Treatment

Prognosis of ES and PERDS is generally good, especially after autologous transplantation, if symptoms are recognized promptly and treatment initiated early in the course.[70] However, allogeneic recipients have poorer outcome. In a recent retrospective single-center study of 927 consecutive first-time allogeneic recipients, 13% (n = 119) developed ES. Patients with ES had significantly higher incidence of grade 2 to 4 acute GVHD and greater nonrelapse mortality (38% vs 19%), as well as poorer overall survival (38% vs 54%) at 2 years post-HSCT.[79] Patients with ES in this study had markedly elevated levels of the biomarker, ST2 of the interleukin-1 receptor family. Interestingly, this biomarker has been strongly associated with treatment-resistant acute GVHD and poor survival.[79,81]

Most patients have symptoms several days to a week before engraftment.[70] Symptoms are often mild and may resolve within 2 to 3 days of onset without specific intervention. Persistent or severe symptoms should prompt consideration of treatment with corticosteroids. Typically, moderate doses (0.5–1.5 mg/kg per day) of intravenous methylprednisolone with tapering of dosage based on clinical response is recommended. Most patients demonstrate rapid clinical improvement with corticosteroid treatment.[70,82–84] Delayed recognition and treatment, however, may lead to death in severe cases.

DRUG-INDUCED PNEUMONITIS

HSCT recipients are exposed to numerous chemotherapeutic agents that have been associated with lung injury. These drugs have been implicated as important risk factors for many of the acute lung injury syndromes discussed earlier in this section. However, isolated drug-specific effects should also be considered in the differential diagnosis of early lung injury. For example, in the 1990s, delayed pulmonary toxicity syndrome (DPTS) described a corticosteroid-responsive pulmonary complication seen exclusively after high-dose chemotherapy (bischloroethylnitrosurea, cisplatin, and cyclophosphamide) followed by rescue autologous HSCT for treatment of breast cancer.[5] In support of drug toxicity as the primary risk factor was the observation that patients who received conventional doses rather than high doses of this chemotherapy regimen had significantly lower rates of DPTS (8% vs 72%).[85] Symptoms of DPTS were nonspecific and included cough, dyspnea on exertion, and fever that developed in most cases within the first 100 days after transplantation.[86] Chest CT scan typically showed ground glass opacities. In cases when surgical lung biopsy was performed, pathologic findings of alveolar septal thickening with interstitial fibrosis, type II pneumocyte hyperplasia, and endothelial cell injury were seen. These findings were consistent, although not specific for drug-induced lung injury.[87] Notably, over the past decade, this treatment approach has fallen out of favor, as several studies failed to demonstrate survival benefit of this high-dose chemotherapy regimen.[88] Over this time period, there have been no additional published reports of DPTS. Although this one specific type of lung injury syndrome is no longer reported, the clinician must be aware of the potential for pulmonary toxicity related to other drugs. Examples of some of the medications that HSCT recipients may receive before or after transplantation with potential to cause pulmonary toxicity include bleomycin, busulfan, methotrexate, sirolimus, amiodarone, cytarabine, chlorambucil, fludarabine, mitoxantrone, rituximab, bortezomib, and thalidomide.[89] Novel immunologic approaches to treating relapsed disease with checkpoint inhibitors (eg, nivolumab, pembrolizumab) targeting the programmed cell death-1 (PD-1) and PD-1 ligand (PD-L1) pathway or infusion of chimeric antigen receptor modified T cells are also associated with systemic inflammation and acute lung injury.[90,91]

CRYPTOGENIC ORGANIZING PNEUMONIA

Cryptogenic organizing pneumonia (COP) is a noninfectious form of lung injury that mimics pneumonia and may occur in the early period after HSCT but is more commonly seen at later time points, with reported median time of presentation at approximately day 100.[92] Clinical symptoms on presentation are nonspecific and include nonproductive cough, fever, and progressive dyspnea. On radiographic imaging, migratory alveolar

infiltrates with bronchovascular and/or subpleural distribution, focal or multifocal ground glass opacities, and linear bands have been reported.[93] Bronchoscopy is helpful to rule out an infectious etiology. If surgical lung biopsy is performed, pathologic findings of plugs of granulation tissues in the alveolar ducts and sacs with associated chronic interstitial inflammation and proximal extension into distal airway lumens is diagnostic.[94] Although COP has been reported after both autologous and allogeneic HSCT, most cases occur after allogeneic HSCT. In a report from the Mayo Clinic of 5340 allogeneic transplantations between 1976 and 1998, 49 cases of COP were identified by surgical lung biopsy. In contrast, only 2 cases were seen in the 1183 patients who underwent autologous transplantation.[94] In a more contemporary review from the Japanese transplant registry of 9550 allogeneic HSCT recipients from 2005 to 2009, 193 cases (2%) were identified.[92] In both studies, grades 2 to 4 acute GVHD was identified as an important risk factor for COP, with the Japanese registry study also reporting increasing HLA disparity, female-to-male transplants, and peripheral blood stem cell source as risk factors. RIC with a fludarabine-based regimen and myeloablative conditioning with busulfan rather than TBI appeared to reduce COP risk.[92,94] COP is generally a steroid-responsive condition. Treatment recommendations for COP are similar to what has been recommended in the nontransplant setting, and involves administration of corticosteroids (eg, 0.5–1.0 mg/kg prednisolone) with slow tapering over months. Patients, however, are at significant risk for disease recurrence or flaring with dose reduction and, overall, patients who develop COP after transplantation have inferior outcomes compared with nontransplant recipients.[92]

ACUTE FIBRINOUS AND ORGANIZING PNEUMONIA

In the past few years, several cases of acute fibrinous and organizing pneumonia (AFOP) have been described in the early and late post-HSCT period.[95–97] AFOP is a rare, distinct type of acute lung injury that requires pathologic evaluation for diagnosis. The presence of diffuse alveolar damage and organizing pneumonia with extensive, diffuse intra-alveolar fibrin deposition without hyaline membranes is characteristic.[98,99] Risk factors and pathogenesis are not known. In the non-HSCT setting, AFOP has been associated with autoimmune disorders, malignancy, infection, and drug toxicity.[97] Patients have been reported to present with cough, fevers, and dyspnea. AFOP may have a subacute or more aggressive course with rapid progression to respiratory failure. On thoracic imaging, reported findings include nodular infiltrates or peripheral and multifocal airspace opacities. Progressive symptoms and radiographic abnormalities despite treatment with broad-spectrum antimicrobial agents should prompt consideration of surgical lung biopsy. Resolution after treatment with high doses of corticosteroids and etanercept has been described.[95,97]

ROLE OF PULMONARY FUNCTION TESTING

Pulmonary function testing (PFT) before transplantation may stratify patients at very high risk for posttransplant respiratory failure and death. In a retrospective study of almost 3000 patients who had undergone allogeneic HSCT at the FHCRC over a 12-year period, 14% developed respiratory failure at a median of 21 days after transplantation.[37] Mortality rate for patients requiring mechanical ventilation exceeded 90%. Pretransplant PFT measurements were evaluated and found to correlate significantly with risk of respiratory failure and death. The investigators found that the combination of 2 PFT variables (forced expiratory volume in 1 second [FEV1] and diffusing capacity for carbon monoxide [DLCO]) had superior discriminating ability for predicting respiratory failure and death compared with any single measurement. The FEV1 and DLCO were used to establish a patient's lung function score, and those with higher scores had the greatest risk. In fact, patients in category IV (FEV1 <60%, DLCO <60%) had an estimated survival of less than 25%.[37] Outcomes were especially poor for patients in categories II to IV if they had received TBI as part of the conditioning regimen.

SUMMARY

Acute noninfectious lung injury syndromes in the preengraftment and early postengraftment period are major causes of nonrelapse mortality after HSCT. Primary risk factors for many of these conditions include toxicity of administered chemotherapy and radiation and the presence of severe acute GVHD in allogeneic recipients. Initial enthusiasm for treating these conditions with high doses of immunomodulatory agents, such as corticosteroids and etanercept, has been dampened by the results of more recent studies, although certain distinct conditions, such as PERDS, may be more responsive to treatment. Pretransplant PFT results can help to risk stratify patients and inform treatment approaches. In the future, novel tools, such as proteomic profiling of BAL fluid or a panel

of biomarkers, may facilitate earlier detection of lung injury and help to distinguish infectious from noninfectious etiologies to perhaps allow for more tailored patient-specific treatment approaches.[100,101]

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