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Complications from Hematopoietic Stem Cell Transplantation that is not Infectious to the Lungs

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Abstract

A prominent cause of morbidity and mortality following hematopoietic stem cell transplant (HSCT) is pulmonary problems. Non-infectious pulmonary problems are becoming a major contributor to transplant-related mortality due to advancements in infection-related complications. Idiopathic pneumonia syndrome (IPS) and bronchiolitis obliterans syndrome (BOS) are the most common early and late consequences, respectively. They can be broadly categorised as either early or late problems. Results from earlier treatments, which mostly consisted of corticosteroids, were frequently poor, stressing the need for a deeper knowledge of the biology of the underlying diseases to direct the adoption of innovative medicines, which are now being used more frequently.

Keywords: Hematopoietic stem cell transplant; Pulmonary complications

Introduction

In the US, around 20,000 autologous and 8,000 allogeneic hematopoietic stem cell transplantation (HSCT) were carried out in 2020, and these figures are rising annually1. With an incidence of 30–40% and an overall mortality of 30%, pulmonary problems following HSCT represent an increasingly significant clinical scenario. In general, these problems can be divided into infectious and non-infectious categories. Their start varies most significantly in connection to the engraftment phase, which is typically classified as occurring either pre-engraftment (days 0 to +30), early post-engraftment (days +30 to +100), or late post-engraftment (days +100 and beyond). Non-infectious pulmonary consequences are a major contributor to transplant-related death as prophylaxis and infection-related mortality have improved. Improvements are being made in the therapy and comprehension of the pathophysiology of several. This review will, if practical, concentrate on incidence with the goal of highlighting some changes in biology, therapy, and prevalence of these clinically [1].

Material and Methods

Symptomless Pneumonia Syndrome

Both autologous and allogeneic HSCT suffer from idiopathic pneumonia syndrome (IPS), which is a significant cause of early transplant-related death. In the absence of a lower respiratory tract infection and hypoxemia, the National Heart, Lung, and Blood Institute defines IPS as the presence of multilobar airspace opacities on chest imaging5. The syndrome includes a broad range of non-infectious diffuse lung injuries, such as peri-engraftment respiratory distress syndrome and diffuse alveolar haemorrhage (DAH) (PERDS).

Total body irradiation (TBI) and high dosage alkylating chemotherapy are key components to the conditioning regimen, which is fundamentally thought to result in IPS for both autologous and allogeneic HSCT. However, significant differences exist between autologous and allogeneic HSCT in terms of IPS incidence, risk factors, and pathogenesis.

For autologous HSCT, pulmonary toxicity from carmustine (BCNU) plays a specific role in the development of IPS, in addition to TBI and other alkylating drugs like cyclophosphamide that are included in the conditioning regimen. The incidence of idiopathic interstitial pneumonitis following autologous HSCT has historically ranged from 4.3 to 16%, with the highest rates observed in patients who had previously undergone chest radiation and in those receiving the CBV (Cyclophosphamide, BCNU, and VP-16) preparative regimen6, 7, 8. Risk variables include age > 559, Hodgkin's lymphoma, female gender, high dosage BCNU, TBI, and conditioning regimen (with greater incidence among CBV, high dose BCNU, and TBI compared to BEAM). Currently, the incidence of IPS in autologous HCT has dropped to 3-6%9 due to the increased use of fractionated TBI, lowered BCNU, and fixed dose busulfan.

Prior to the advent of nonmyeloablative and decreased intensity conditioning for allogeneic HSCT, 10–20% of idiopathic interstitial pneumonias were reported within 100 days following transplant. Myeloablative conditioning, TBI dose, high-grade acute graft versus host disease (aGVHD), advanced age, and transplant indication are risk factors; patients with AML and MDS have a higher likelihood of developing these conditions. The incidence of IPS has decreased to 1-8%3, in the current period due to stricter diagnostic criteria, more sophisticated diagnostic methods, and increased use of reduced intensity conditioning (RIC). Indeed, in relatively recent cohorts13, it was shown that the cumulative incidence of IPS was significantly lower in patients receiving nonmyeloablative conditioning compared to conventional (i.e. myeloablative) conditioning, highlighting the significance of conditioning intensity in the development of IPS [2, 3].

Alveolar Haemorrhage, Diffuse

Conventionally, DAH is identified by progressively bloodier BAL results in acute cases or by an increase in the number of macrophages carrying hemosiderin in subacute or chronic cases27. It is a unique

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IPS subtype. The incidence is only up to 5% of patients22, which is comparatively low. It most frequently happens prior to engraftment, though it can also appear early after engraftment, just like in IPS more broadly.

Myeloablative TBI, umbilical cord blood (UCB) HSCT, delayed engraftment, or graft failure28 are risk factors for development. Most of the aetiology is still unknown. Possible contributing factors include lung injury brought on by the pre-transplant conditioning procedure, the activation of alloreactive T cells, and subsequent immune-mediated injury (in this case to the pulmonary microvasculature). These underlying mechanisms were previously identified for IPS. Thrombocytopenia and coagulopathy are some other variables that may specifically contribute to DAH. In fact, this helps to understand how important graft kinetics is to overall risk.

When hypoxemia, multi-lobar pulmonary opacities, and occasionally hemoptysis are present in the appropriate clinical situation and there are centrally positioned ground glass opacities on CT, DAH is frequently suspected. The earlier mentioned BAL results and the exclusion of infection are necessary for the diagnosis.

Respiratory distress syndrome during peri-engraftment

The symptoms of peri-engraftment respiratory distress syndrome (PERDS) include hypoxic respiratory failure, bilateral pulmonary infiltrates, and an onset period of 11 days on average, usually within 5 days of engraftment35. It belongs to the larger category of engraftment syndrome (ES), along with symptoms like fever, rash, and systemic capillary leak. In both autologous and allogeneic HSCT37, the incidence is up to 5%.

Allogeneic HSCT, TBI, busulfan, G-CSF, and cyclophosphamide are risk factors for PERDS and ES38, 39, 40, and 41. Recently, cancer patients receiving autologous HSCT who had had anti-PD-1 therapy and a history of pulmonary disease were also independent risk factors for PERDS41. It is believed that a key factor in the aetiology of PERDS is the migration of neutrophils into the lungs after engraftment and the subsequent production of proinflammatory cytokines. Since it is regarded as a subset of IPS, the disease is likely fundamentally based on comparable pathophysiological mechanisms, such as prior lung injury, inflammation, and recruitment of immune effector cells.

Ground glass opacities, peribronchovascular consolidations, interlobular septal thickening, and pleural effusions are typical non-specific radiographic findings (Figure 4), but identification is suspected in the proper clinical situation with additional capillary symptoms [4].

Syndrome of Bronchiolitis Obliterans

An important subset of chronic graft-versus-host diseases (cGVHD) that affect the lungs is bronchiolitis obliterans syndrome (BOS). Historically, incidence ranged between 2-19% in primarily small case series during the period before decreased or non-myeloablative conditioning. The current incidence is thought to be between 6.5 and 9%51,52. After day 100 and frequently within two years of transplantation, BOS commonly manifests itself at a median interval of 273 to 547 days [5, 6].

Current risk factors include the following: the dose of cyclophosphamide, the absence of ATG in conditioning (with the absence of ATG increasing risk), busulfan-based conditioning, the presence of cGVHD, peripheral blood stem cell (PBSC) transplant, female donor to male recipient transplant, prior interstitial pneumonitis, prior viral and/or bacterial pneumonia, and lower pretransplant FEV1/FVC54, 55, 56, 57. Comparing myeloablative conditioning to reduced or non-myeloablative regimens has indicated that myeloablative conditioning specifically increases the cumulative risk of BOS [7].

Discussion

Although not unique to HSCT, transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) are important causes of acute lung injury, particularly in the peri-engraftment period when transfusion burden is high. The acute onset pulmonary edoema (not caused by left atrial hypertension) with hypoxia and no additional risk factors for acute respiratory distress syndrome (ARDS) occurring within 6 hours of the conclusion of the transfusion is known as TRALI, according to the Canadian Consensus Criteria115. Within six hours following the end of the transfusion, TACO is characterised as acute respiratory distress and/or pulmonary edoema with evidence of cardiovascular alterations, including fluid overload (high central venous pressure, signs of left heart failure), and/or elevated B-type natriuretic peptide [8].

Conclusion

Non-infectious pulmonary problems after HSCT are now a significant contributor to both early and late transplant-related morbidity and mortality due to advances in supportive care and antimicrobial prophylaxis. Importantly, nothing is known about the pathophysiology of many of these entities. For many of them, corticosteroids continue to be the mainstay of treatment; nevertheless, the poor outcomes observed in disorders like IPS and pulmonary cGVHD underlie not just the need for more effective and tailored therapeutics, but also for enhanced mitigation and prevention efforts [9].

Thankfully, a number of these targeted drugs are currently being examined and licenced in the modern period. Axatilimab, baricitinib, pomalidomide, imatinib, and others are among the new medications being actively researched for the treatment of cGVHD in addition to those already covered here. These medications may also be useful in treating pulmonary GVHD. To continue researching such medications and enhance patient outcomes following HSCT, more trials are urgently required.

In order to balance the best disease control with transplant-related mortality, it is still important to carefully choose the conditioning regimen and intensity for patients who are thought to be at higher risk in order to reduce non-infectious pulmonary problems after HSCT. Agents like MSC may have a function in prevention for early-onset problems like IPS based on pre-clinical grounds and require further study. Tocilizumab, which may be helpful in aGVHD prophylaxis123, may also be helpful in lowering the incidence of IPS in high risk groups given the probable involvement for IL-6 in the aetiology of IPS. Only early detection and rapid use of "topical" therapy are now expected to lessen the severity of these debilitating illnesses. No medical therapies have shown efficacy in prophylaxis for late non-infectious pulmonary complications like BOS [10].

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Conflict of Interest

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