Pulmonary complications after hematopoietic stem cell transplantation in children: a functional and tomographic evaluation

Débora Carla Chong-Silva, Pollyana Moreira Schneider, Tyane de Almeida Pinto Jardim, Samantha Nichele, Gisele Loth, Carlos Antônio Riedl, Herberto José Chong Neto, Carmen Maria Sales Bonfim, Nelson Augusto Rosário Filho

TO THE EDITOR,

Hematopoietic stem cell transplantation (HSCT) is the treatment of choice for neoplastic and non-neoplastic diseases in children, and despite advanced supportive care and specific treatments, pulmonary complications still occur in a large proportion of all hematopoietic stem cell recipients, accounting for considerable morbidity and mortality.

Etiologically, these complications can be organized according to the time elapsed since transplantation. In the pre-engraftment phase (first 30 days after the procedure), non-infectious complications and fungal pneumonia are more common. In the early stage (first 100 days), viral infections are frequent, especially cytomegalovirus, although non-infectious complications, such as pulmonary edema and idiopathic pneumonia syndrome, can also be observed. In the late stage (after the first 100 days), the main complications are associated with chronic graft-versus-host diseases (GVHD), such as bronchiolitis obliterans (BO) and BO with organizing pneumonia.

Pulmonary function tests (PFTs) can help identify the level of deterioration in the post-HSCT period. Although computerized tomography (CT) scanning is the method of choice for detecting pulmonary abnormalities, CT scan findings are generally nonspecific and require clinical and temporal correlations based on the patient’s immunological status.

A retrospective review was performed on all the under 14-year-old patients who received HSCT at a referral center from 2013 to 2017, regardless of the underlying diseases that prompted the indication for transplantation. The study was approved by the Ethics Committee for Research Involving Human Beings of CHC-UFPR, under protocol number CAAE: 87629118.3.0000.00.

One hundred and sixty-one patients were transplanted in the analyzed period and had their medical records scrutinized. One hundred and six patients (65.8%) were male, and the mean age was 7.9 ± 4 years old. Additionally, 143 (88.8%) received a single transplant, 14 (8.7%) received two transplants, and 4 (2.5%) received three transplants. Among the 143 single transplant patients, 92 (57.1%) had non-related donors.

After HSCT, 44 (27.3%) patients sustained 69 events of pulmonary complication. Of these, 26 patients (59.1%) had one pulmonary complication, 13 (29.5%) had two, 3 (6.8%) had three, and 2 (4.5%) had four.

Post-transplant PFT was conducted in 79 (49.1%) children, 35 (44.3%) of whom had functional changes identified at clinical follow-up. Nonspecific ventilatory defects were found in 52 (65.7%) patients, while 20 (25.7%) had mild obstructive ventilatory disorder, 2.9% had severe obstructive ventilatory defects, and 5.7% confirmed restrictive ventilatory defects.

Chest CT was performed in 75 (46.6%) patients in the post-transplant follow-up, 61 (81.3%) of which presented abnormalities. The findings and frequencies were nodules in 52.5% of the cases; atelectasis in 34.4%; ground-glass opacification in 34.3%; mosaic attenuation patterns in 27.9%; ground-glass halo nodules in 23%; bronchial thickening and consolidation, both in 16.4%; lymph node/lymphadenomegaly in 14.8%; tree-in-bud patterns in 11.5%, and other findings (pleural effusion, interlobular septal thickening, and bronchiectasis) in 50.8%.

Chronic pulmonary disease was observed in six (3.7%) patients, three with diagnoses of pulmonary veno-occlusive disease and three with bronchiolitis obliterans (BO).

Death as an outcome occurred in 31 (19.3%) cases. The cause was predominantly pulmonary in nine (29%) of the deaths, which included invasive aspergillosis in three (33.3%), cytomegalovirus pneumonitis in three (33.3%), herpetic pneumonia in one (11.1%), both aspergillus and cytomegalovirus pneumonitis in one (11.1%), and undefined respiratory failure in one (11.1%).

There were no significant differences concerning age, sex, or donor type among patients who had developed pulmonary complications after HSCT. A significant association regarding the presence of pulmonary complications was observed in those undergoing more than one transplant (p=0.009).

No significant associations were found between the occurrence of chronic pulmonary disease (pulmonary veno-occlusive disease or BO) and the variables analyzed (age, sex, type of donor, and number of transplants).

1. Serviço de Alergia, Imunologia e Pneumologia Pediátrica, Universidade Federal do Paraná, Curitiba (PR), Brasil.
2. Departamento de Pediatria, Universidade Federal do Paraná, Curitiba (PR), Brasil.
3. Unidade de Transplante de Medula Óssea, Universidade Federal do Paraná, Curitiba (PR), Brasil.

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This study aimed to describe the leading post-transplant pulmonary complications in children by analyzing the patients’ characteristics and the possible factors associated with the occurrence of such complications.

Viral and fungal infections were the most prevalent causative agents, contradicting other studies (2-4,9) in which bacterial infections were the most common. Such divergence may be related to the large number of autologous transplants in other studies; our study included only allogeneic transplants, where opportunistic infections are more common due to prolonged immunosuppressive therapy.

As for non-infectious post-HSCT complications, non-cardiogenic pulmonary edema was also prevalent. Usually, this condition can be related to pulmonary toxicity induced by drugs, sepsis, aspiration, hemoderivative transfusion, acute GVHD, or heart disease after total body irradiation. (1,2,4)

Changes in pulmonary function were seen in approximately half of the patients submitted to spirometry, and nonspecific ventilatory defect (NVD) was the main finding. Spirometry findings vary in transplanted children. Srinivasan et al. (2017) found that obstructive defect was the primary finding (43%), followed by restrictive (25%), mixed (5%), and normal lung function (27%) in children with a median of 5 years post-HSCT. (10) Jung et al. (2021) showed that changes in FEV1 in the first 3 months after BO diagnosis impacted outcomes such as death and lung transplantation, indicating the need for earlier monitoring and interventions to change survival indicators. (7)

The chest CT abnormalities found in the present study were highlighted in previous reviews, particularly airspace consolidation, ground-glass attenuation, and nodules. (8,9) These findings are important markers for the differential diagnoses of lung conditions, some of which are typical of specific clinical scenarios. (8,9)

Pulmonary veno-occlusive disease and BO were diagnosed in 1.8% of the patients in this study. Characterized by an impairment of the small airways, BO is described as a primary late non-infectious pulmonary...
syndrome after allogeneic HSCT that usually presents after the first 100 days after HSCT.\(^2\) It is most frequently described after conventional myeloablative regimens and busulfan-based preparative regimens.\(^3\) One limitation of our study was the lack of pre-HSTC data collection; such information would likely explain the results. Other known BO risk factors include a lower baseline FEV1/FVC ratio, non-Caucasian ethnicity, lower circulating immunoglobulin G levels, conditioning with busulfan, non-related donors, and female donors.\(^3\)

This review illustrates the size of the problem, in which pulmonary complications occurred in 27.3% of the patients and death in 19.3% of the cases in children transplanted at the referral center.

Pulmonary complications after HSCT in children are relevant causes of morbidity and mortality in this group of patients. Knowing the main events, the patient's profile and the factors involved comprise the first step in designing strategies for the prevention and management of these complications.

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