EDITORIAL

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Inhaled Bronchodilators and Corticosteroids in the Management of Bronchiolitis Obliterans due to Allogenic Hematopoietic Stem Cell Transplantation

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The prevalence of blood disorders that require stem cell transplantation is rising worldwide.[1] In the Eastern Mediterranean Region (EMR), the relative prevalence of inherited blood disorders such as thalassemia is higher than the world average.[2] In Oman, nearly half of the cases that require transplantation are inherited.[3] Following the worldwide trend, hematopoietic stem cell transplantation (HSCT) is being increasingly preferred in Oman and its neighboring countries, due to a greater likelihood of cure.

However, HSCT has its own risks. Pulmonary complications are important causes of morbidity and mortality in patients undergoing this procedure. Bronchiolitis obliterans (BO) is the most frequent noninfectious pulmonary complication due to HSCT. The characteristics of BOS are the new onset of dyspnea or airflow limitation observed on lung function testing by spirometry, evaluating the forced expiratory volume in one second of expiration (FEV_1), and the presence of a mosaic pattern on computed tomography (CT), indicating air trapping related to airflow limitation.[4]

The first report goes back to 1978, when lymphocytic bronchitis in 10% of autopsies from patients who died following HSCT was described.[5] BO is typically thought as a manifestation of graft vs. host disease (GVHD) affecting the respiratory system, with an incidence of 2–3% in allogeneic HSCT recipients leading to lung function decline and poor quality of life.[6]

In past years, a diagnosis of BO after HSCT presented with nearly universal mortality in the absence of consensus for diagnostic guidelines, poorly understood pathogenetic mechanisms, and limited studies of therapeutic or supportive care strategies.[7] The current consensus offers more accurate diagnostic criteria and greater understanding of underlying mechanisms of the disease.[7]

However, despite such improved understanding, BO continues to confer a poor prognosis.[3] Immunosuppressive therapy has been used for the treatment of BO as a part of the treatment for GVHD. However, no specific effective therapy improving the outcome of BO has been identified.[8] Azithromycin has been evaluated in small clinical trials of patients with BO after HSCT, showing some benefit in pulmonary function tests,[9] while novel agents such as leukotriene inhibitors, statins, N-acetylcysteine (an antioxidant), and nintedanib (a tyrosine kinase inhibitor) have been mentioned as possible therapies.[10–12]

At present, no randomized controlled trials suggesting an effective treatment have been

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completed. Systemic corticosteroids in combination with other immunosuppressive agents continue to be the cornerstone of the treatment strategy for BO.[13]

The aim of this editorial is to discuss whether inhaled bronchodilators and corticosteroids are effective in the management of BO following HSCT, through the results of the studies that had been performed in the recent years.

Inhaled bronchodilators and corticosteroids are safe and effective for patients with pulmonary airway diseases such as asthma and chronic obstructive pulmonary disease (COPD), and improve their quality of life and survival odds.[14] Airways abnormalities in COPD include chronic inflammation and narrowing of small airways as well as reduction in their numbers, characterized by the presence of CD8+ T-lymphocytes, neutrophils, and CD68+ monocytes/macrophages.[15] The T-cell population infiltrating the airways in patients with asthma is characterized by the T-helper 2 subset of lymphocytes that produces specific cytokines, such as interleukin (IL)-3, IL-4, IL-5, and IL-13, when stimulated with antigen, and expresses the chemokine receptors (CCR4 and CCR8), and the chemoattractant receptor (CR)-like molecule, a receptor for prostaglandin D2.[16] BO is characterized by inflammation and narrowing of the small airways. Pathogenesis of BO is still unclear but reported mechanisms have focused on donor T-lymphocytes, inflammatory mediators, and cytokines such as IL-1, IL-6, IL-8, IL-18, and tumor necrosis factor-a.[4]

Very few studies refer to the role of inhaled bronchodilators and corticosteroids in the management of BO following HSCT. It has been reported that with the use of inhaled steroid and long-acting bronchodilator combination, formoterol/budesonide in patients with mild to moderate BO after HSCT, without other modification of their immunosuppressive therapy, was correlated with significant improvement in FEV_1 values during follow-up of the patients.[17,18]

In addition, the efficacy of high-dose inhaled corticosteroids, high-dose inhaled steroids, and long-acting bronchodilator combination in the treatment of BO, has been evaluated. According to a study, patients who received high-dose inhaled fluticasone propionate, an inhaled corticosteroid, presented with FEV_1 stabilization 3–6 months after treatment, indicating that high-dose inhaled corticosteroids may be effective in the treatment of BO due to HSCT.[19] In another study, patients with BO following HSCT already receiving low-dose budesonide/formoterol (160/4.5 μg bid), received high-dose budesonide/formoterol (320/9 μg bid) with no significant differences in FEV_1 values comparing the periods of before and after increasing the dose of budesonide/formoterol. This observation suggests no superior effect of high-dose budesonide/formoterol compared with low-dose in lung function estimated by the evaluation of the FEV_1.[20]

Moreover, the corticosteroid exposure and lung function in eight patients with BO who were treated with a combination of inhaled fluticasone, azithromycin, and montelukast (FAM), and a rapid corticosteroid taper have been reviewed for six months retrospectively. There was a comparison of these patients to 14 matched patients who received therapy with high-dose corticosteroids followed by a standard taper. The researchers found that prednisone exposure in FAM patients was one-quarter that of a retrospective matched group of patients, with minimal change in median FEV_1, suggesting that BO may be spared the morbidities related to long-term corticosteroid therapy by using different agents without many side effects.[21]

The combination of inhaled FAM as a potential treatment for BO after HSCT has also been evaluated in a phase II, single-arm, open-label study. In one study,[22] 36 patients received the combination of FAM with a brief steroid pulse. The main result that was measured at the end of this study was treatment failure, defined as a 10% or greater FEV_1 decline at three months. At three months, 6% of the patients had treatment failure compared to historical controls, of whom 40% had treatment failure. Steroid dose was reduced by ≥ 50% at three months in 48% of patients who could be evaluated.

The therapeutic impact of budesonide/formoterol, montelukast, and N-acetylcysteine in patients with BO after HSCT has also been studied. In one study, 61 patients received the combination of budesonide/formoterol, montelukast, and N-acetylcysteine for three months. After three months of treatment, mean FEV_1 showed improvement. This result demonstrated that inhaled budesonide/formoterol in combination with montelukast and N-acetylcysteine improved lung function.[23]

In our opinion, treatment with inhaled bronchodilators and corticosteroids, standalone or in combination with other agents such as

azithromycin, montelukast, and N-acetylcysteine, may be useful for the management of BO following HSCT, as it has been reported in small studies that improve lung function values and respiratory symptoms. Furthermore, they are localized to the target organ and allow systemic corticosteroids dose reduction, leading to fewer adverse effects. However, additional studies are required in order to clarify the role of inhaled bronchodilators and corticosteroids in patients with BO after HSCT.

At this stage, we recommend clinicians in Oman, Eastern Mediterranean Region, and the rest of the world to investigate whether inhaled bronchodilators and corticosteroids help improve lung function among their patients who contracted bronchiolitis obliterans post allogeneic hematopoietic stem cell transplantation.

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