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Research Article

Post-Allogenic Hematopoietic Stem Cell Transplantation Bronchiolitis Obliterans in Pediatric Age group Patients: Literature Review

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Abstract

Bronchiolitis obliterans and bronchiolitis Obliterans syndrome (BO/BOS) are one of the common and lethal pulmonary complication after allogenic hematopoietic stem cell transplantation (HCT). BO/BOS after HCT are associated mainly with chronic graft versus host disease (cGVHD), with other risk factors related to the type of donors, the pre-transplantation myeloablation therapy and post transplantation care identified to play an important role. As there is no definitive curative treatment for BO/BOS, the main goal for clinicians should be to prevent and to screening for and early diagnose those pathological entities. Decline of pulmonary function test parameters from the pretransplantation one or from the latest post-transplantation PFT with an obstructive pattern is usually the first sign to be noticed. The high morbidity and mortality rates among post-HCT patients with BO/BOS make it a priority for more scientific research efforts to overcome the challenges in diagnosis and effectively treating those subgroups of patients. This review provides detailed revision of the literature covering the well- established facts of post-HCT BO/BOS in pediatric age group patients as well as the future directions and novel therapies. While a lot of studies done on adult cohorts, studies that involving pediatric patients is still limited. The main areas in need for more research efforts was also identified in our conclusion.

Keywords: *Bronchiolitis Obliterans; Bronchiolitis Obliterans Syndrome; Allogeneic Hematopoietic Cell Transplantation; Pulmonary Chronic Diseases; Chronic Graft Versus Host Disease*

Introduction

HCT

Allogeneic hematopoietic cell transplantation (HCT) is the treatment of choice for a wide range of hematologic and immunological disorders and it includes transplantation of hematopoietic progenitor cells from a range of sources (e.g. bone marrow of related or unrelated donors, peripheral blood, or cord blood) after a preparative conditioning regimen. Pulmonary complications such as the idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, bronchiolitis obliterans, and late-occurring infections are a common source of morbidity and occasionally mortality after this procedure. Occurrence of post-HCT pulmonary complications in pediatric age group patients was reported to be 25% in a previous retrospective study [1].

BO/BOS

Bronchiolitis Obliterans (BO) is one of the most common post-HCT pulmonary complication and is demonstrated by development of small airway inflammation and narrowing owing to fibrous scar. These changes manifest as airflow limitation in the clinical setting. The term bronchiolitis obliterans syndrome (BOS) is used when a patient has airflow limitation on spirometry in the absence of other etiologies', however histopathological diagnosis to document BO is not available. BOS was reported to be the second most common noninfectious pulmonary complication (6.1%) in a recent Turkish study [2].

In this literature review we aim to evaluate and summarize the existing evidence regarding BO as a post-HCT complication in terms of incidence, risk factors, prevention, clinical features and diagnosis, treatment, and outcome.

Methods

A comprehensive search limited to English language was performed using PubMed applying the following search terms: (Hematopoietic Stem Cell Transplantation) and (Bronchiolitis Obliterans) and (Pediatric) in various combinations. The search was conducted using these terms in the keywords, titles and abstracts.

The articles were first scanned based on the title and abstract and were classified into three groups (include, exclude or unclear). The full-text version of all unclear articles was checked and subsequently classified in one of the two other groups (include or exclude).

All manuscripts were assessed for inclusion criteria written in English, included pediatric age group (0 - 21 years old) cohorts, published in the 2005 - 2022 period and covering the scope of this literature review.

Results

Study characteristics

The literature search identified a total of 64 articles. Forty-Four articles were excluded as they do not fulfil the above-mentioned inclusion criteria. Some articles from adult data are used for the sake of completion of this review.

Incidence

Mild Impairment in lung function test is frequent following HCT but are rarely symptomatic. Pulmonary assessment 10 years after allo-HCT of 35 children transplanted between 2000 and 2004 was done by Sophie L'excellent., *et al*. The thirty-five participants answered a questionnaire regarding if they had pulmonary symptoms, and pulmonary function tests (PFT's) were performed. One-third of asymptomatic children [3] in the cohort showed abnormal pulmonary function test (restrictive pattern). However, more sever PFT parameters decline and any child with respiratory symptoms after HCT required more detailed and closer follow up. In a recent Turkish study, 71 out of 195 post-HCT pediatric patients (36.4) developed pulmonary complications [2]. BOS was reported as the second most common non-infectious pulmonary complication (6.1%) [2]. In other studies, the incidence was between 2.7% and 14.2% [3-7]. In an interesting study by Manuela Fernández-García., *et al*. BOS was the reason for PICU admission in four (5.9%) out of the total 68 patients that required intensive care post HCT, two of them deceased.

Risk factors

As there is no known etiology identified for BO/BOS, yet many risk factors have been studied and well-described. On the top of the list is the chronic graft-versus-host disease (cGVHD), high-risk underlying disease, pre-existing pulmonary conditions, viral infections and the myeloablative conditioning prior to allo-HCT.

cGVHD

BO is believed to be an immune-mediated lung injury, and in pediatric patients it is mostly seen following HCT in association with chronic graft-versus-host disease (cGVHD). Hence, immunosuppression non-adherence is considered a significant risk factor for BO/BOS [34].

With regards to post-Lung transplantation pediatric patients, a comprehensive review of single-center studies of BO/BOS found that acute rejection episodes occurring > 3 months post-transplant and lymphocytic bronchitis/bronchiolitis, especially > 6 months post-transplant, were the most consistent risk factors [34]. In a study by CN Duncan., *et al*. all post-HCT children who were diagnosed with BO suffered from cGVHD (18 out of 18) [5].

Donor-type

Another important risk factor that is addressed frequently in the literature is the type of donors. In the previous mentioned retrospective study 14 of 18 patients with BO/BOS received stem cells from unrelated donors [5]. However, Other studies found that the source of stem cells is not statistically significant risk factor [2,6,7].

Allergic/anaphylactic reactions

Other interesting observation in the same study [5] is that in total 5 of 18 (27.8%) patients with BO/BOS have either an anaphylactic reaction to a drug, toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS) during the first 100 days following HCT. This compares with four (2%) patients in the non-BO/BOS group (P value less than 0.001). No patients without BO/BOS had SJS or TEN.

The underlying disease

Patients with high-risk underlying disease (i.e. blood malignancies and severe primary immunodeficiency) [5,6] and pre-existing pulmonary conditions [11] were more prone to develop BO/BOS.

Viral infections

Community-acquired respiratory viruses (RV) including paramyxoviruses, influenza and adenovirus, have been implicated in BO/BOS [34]. In a prospective study published in 2009, in multivariate analysis of risk factors, only respiratory viruses (RV) positivity remained a predictor for the development of BOS and other alloimmune lung syndromes (allo-LS) (P value = .007). The median time from RV positivity and the development of allo-LS was 7 weeks (range, 1.2 - 20 weeks) [8].

The timing of development of RV positivity seems to be important as well. Patients who were positive early after transplantation (before the median of day 116) had a slightly greater likelihood of developing allo-LS than those who became RV-positive after day 116 (P value= .089) [8]. Univariate analysis of the influence of HCT-associated complications on allo-LS showed that adenovirus reactivation (P value = .004) was predictive of allo-LS [8].

Myeloablative conditioning-type

Myeloablative conditioning prior to allo-HCT, with either total body irradiation (TBI) or busulfan-based conditioning, has been reported as a contributing factor for pulmonary toxicity including BO. In a recent study which included 129 hematological malignancies, pediatric patients underwent HSCT between 2003 and 2014 [9]. TBI dose rate significantly affected development of overall pulmonary toxicity (P = 0.2).

Other study showed that, both regimens of busulfan-cyclophosphamide and busulfan fludarabine were related to pulmonary toxicity, with the latter found to be less toxic [10]. The comparative data between different conditioning regimens in pediatric HCT are limited and with contradictory results [11,12].

Prevention

As studies show, BOS is uncommon but very severe and irreversible pulmonary complication of HCT and every effort should be done to initially prevent and then detect early those sub-group of patients. Pre-emptive and prophylaxis therapy to prevent GVHD and respiratory tract infections, early investigation and diagnosis of any post-HCT child with respiratory symptoms can both improve the outcome of HCT [13]. Other areas for more research efforts to establish their benefits vs risks are the practice of T cell-depleted HCT and reduced intensity conditioning regimens [13].

The use of umbilical cord blood as a source of stem cells is increasing, especially in children. Stem cells in cord blood are relatively immature and, therefore, may decrease the incidence of GVHD. In a preliminary result, a retrospective study showed that none of the 58 patients (mostly children) who received umbilical cord blood stem cells developed chronic GVHD and bronchiolitis obliterans [14].

Diagnosis

Lung biopsy is the gold standard test to diagnose BO. Fibroproliferative obliteration of small airways, dense eosinophilic sub-mucosal fibrosis in the bronchioles and partial (concentric or eccentric) or complete luminal occlusion are seen on the biopsy. Destruction of the airway wall and surrounding smooth muscle may also be present [34]. Due to its extensive nature and risk of bleeding, the clinical diagnosis of BOS is based on pulmonary function test (PFT) abnormalities including: FEV1 < 75% predicted and fixed obstructive FEV1/FVC ratio, and evidence of air trapping or small airway thickening or bronchiectasis on high-resolution computed tomography, residual volume 120% of predicted along with absence of active infection.

A randomized double-blinded study of adult patients with newly diagnosed BOS showed that inhaled budesonide/formoterol had a statistically significant effectiveness, and it can increase the FEV1 after 1 month of therapy, and the improvement was maintained after 6 months of therapy [15], while this intervention is not being studied yet on children cohort, but still, it is supporting the concept that earlier recognition of disease and intervention may improve outcomes.

Earlier recognition of BOS requires routine screening of asymptomatic patients to detect a decline in lung function. The most recent recommendations by National Institutes of Health (NIH) 2020 consensus project [16] work on the diagnostic challenges of the previous report of 2014 and reported the following:

1. Routine PFTs for all HCT recipients (even asymptomatic) should be performed pretransplant and then every 3 months for at least 1 year after HCT. Full PFTs, which include spirometry, lung volumes, and diffusing capacity of carbon monoxide, should be obtained when feasible at pre-HCT baseline, D100, and at 1 year post-HCT. Limited spirometry can be substituted for full PFTs at 6 and 9 months post-HCT. For patients with newly diagnosed chronic GVHD, it is recommended that spirometry be obtained every 3 months. Alternative approaches to lung function are needed for evaluation of younger patients unable to perform PFTs to provide equivalent screening functionality.

2. Patients with documented respiratory viral infections and concomitant FEV1 decline should be considered high risk for BOS and followed with serial PFTs (or spirometry) at short time intervals. Currently, the diagnosis of BOS, requires absence of infection in the respiratory tract documented with clinical investigations, including microbiologic testing, but patients with chronic GVHD often have persistent viral shedding and frequent recurrent infections.

3. Asymptomatic decline in FEV1 may be indicative of early BOS or other pulmonary disease. A decline in FEV1 of 10% from pre-HCT baseline, or the immediate prior spirometry, in an asymptomatic patient should be followed up clinically with close interval spirometry or further workup.

However, even with the 1 year follow up with PFTs screening still some patients can be missed as they develop BOS after the first 12 months post-HCT [17]. Future studies are needed to help in the development of a new screening protocol that can subsequently be evaluated.

Defining a "pre-BOS" stage that characterizes airflow obstruction in patients before the development of clinical symptoms is another critical aspect that need more research effort. In adult HCT recipients, a 10% decline in FEV1 and/or a 25% decline in FEF 25 - 75% compared to pre-HCT baseline has been shown to be sensitive for the prediction of BOS (85%) [18].

Early post-transplant declines in FEF 25 - 75% are strongly associated with the development of BOS after HCT and may be more important than FEV1; therefore, both should be monitored and compared when developing an early diagnostic strategy [18].

Even with the classic BOS picture characterized by loss of lung function (FEV1) it is still important to differentiate between BO/BOS and other pathological entities that can be part of the same spectrum of the disease. An important subset of the patients will have improvement in FEV1 following administration of a macrolide, such as azithromycin. These patients are typically referred to as having "neutrophilic reversible allograft dysfunction" or "azithromycin-responsive allograft dysfunction. Typically, they will show BAL neutrophilia [34].

Potential cytokines and cellular injury markers such as endothelial markers, extracellular matrix proteins, and lung surfactant/lung proteins (i.e. serum surfactant protein D, profibrotic cytokines, such as transforming growth factor Beta214 or platelet-derived growth factor, matrix metalloproteinase 2/3/7/8/9) have all been reported as prognostic measures mainly in adult patients [19,20,34]. Validation studies in pediatric-age group patients is an important area to explore.

Novel radiographic techniques have been investigating to aid in early detection of the disease in asymptomatic post-HCT pediatric patients, in an interesting paper published in 2019, 129Xe MRI provides a reliable imaging-based assessment of pulmonary involvement in this potentially difficult to diagnose pediatric population [21].

First-line treatment

Despite several treatment strategies have been discussed in the literature, there is no randomised controlled trial that has described a long-lasting effect of any treatment option for BO/BOS after HCT, and the treatment is based on clinical experience and observational data.

Many experts use high-dose inhaled glucocorticoids (e.g. budesonide ≥ 720 mcg/day, fluticasone propionate ≥ 440 mcg/day) at the onset of mild airflow limitation (forced expiratory volume in one second [FEV1] ≥ 70 percent predicted, but < 80 percent). For those patients who continue to have FEV1 decline and symptoms on inhaled glucocorticoids + or -LABA. Regimen will expand to "FAM" therapy (i.e. inhaled fluticasone 440 mcg twice daily, azithromycin 250 mg three times weekly, and Montelukast 10 mg daily). This is based only upon small studies (mainly adult patient's data) that demonstrate low-risk and some evidence of FEV1 stability [22,23].

Montelukast has been studied in a pediatric-cohort prospective trial, its phase II results showed that Montelukast was well tolerated and in none of the patient's there was any escalation of therapy required. All 23 patients except 1 patient had stable or improved FEV1 slope. In those with a > 5% improvement in FEV1, clinically significant progression was seen in the scores of breathings, energy, and mood [24].

Using high dose systemic steroids (Pulse therapy) approach resulted in a stabilization of the lung function and limited side effects and it may present a treatment option especially in severe cases [25,26].

Second-line treatments and future directions

Other immunosuppressant agents also showed promising results as a second-line therapies, despite the need for other prospective studies to confirm these results. As shown in this study where the overall response rate in the 13 BO patients who received imatinib mesylate (IM) was 76.9%. Four years after HSCT, overall survival (OS) was 42.6% (95% CI, 18.2 - 65.3) in the group without IM and 83.3% (95% CI, 27.3 - 97.5) in the group with IM [27].

Calcineurin inhibitors and antithymocyte globulin for treatment of bronchiolitis obliterans is well established and may stabilize lung function in 30 - 50% of patients. Other promising agents under investigation to improve the outcome of bronchiolitis obliterans include extracorporeal photochemotherapy (Photopheresis) [13,34].

In an early experimental study, a murine post-HCT BO model was treated with pirfenidone from days 28 to 56 post-transplantation. Pirfenidone treatment significantly reduced lung fibrosis ($P < .01$) to comparable lung function with BM-only mice which can provide a rationale for the consideration of future clinical trials for pirfenidone as cGVHD therapy in patients particularly those that have BO, a devastating complication of allo-HSCT [27].

Bone marrow derived, multipotent mesenchymal stem cells (MSCs) can give rise to a broad range of tissue cells, including the lungs. Studies have shown that intravenous or intratracheal injection of MSCs is protective in experimental models of lung injury [28]. MSCs are also effective in ameliorating GVHD and were recently shown to reverse airway obstruction in the Post HBSC BO mice model [29].

Outcome

In a retrospective study, PFTs were gathered during the 24 months after BOS diagnosis in 21 children underwent HCT, the change in FEV1 during the first 3 months after BOS diagnosis was significantly different between the good and poor outcome groups. It was concluded that, the phase immediately following BOS diagnosis, is the most critical in determining BOS outcomes. These results suggest that an active intervention strategy is needed during the first 3 months after BOS diagnosis to improve patient prognosis [30].

Some patients with refractory BO/BOS due to chronic GVHD respond partially to glucocorticoids and increased immune suppression, but often BOS is irreversible and the patient can progress to hypercapnia and respiratory failure. Adult data showed that lung transplantation can be the option in selected cases [31], limited pediatric -age group data available.

A major and under-recognized complication in the patients with BO/BOS is pulmonary hypertension (PH). In a small case report of 4 patients, 3 out of 4 developed PH after the diagnosis of BO at a median of 91 days (range 46 - 833 days). The three patients diagnosed with PH and BO were administered myeloablative conditioning regimens, while the one patient without PH was administered a reduced intensity conditioning regimen. All four patients had a history of chronic GvHD at the time of BO diagnosis. This study was limited by a small sample size and further work needed to determine the incidence and clinical features of PH in this subgroup of pulmonary complicated cases [32].

As showed in the previous reviews, Post-HCT BO/BOS is a severe disease with high morbidity and mortality rates. Despite the proper diagnosis and treatment, mortality rate was between 21.5% to 38.8% [5,30,32] and up to 60% in different study [6].

Conclusion

While a lot of studies done on adult post-HCT BO/BOS cohorts, studies that involve pediatric patients still limited. Main areas in need for more research efforts include the optimum source of hematopoietic stem cells and conditioning regimens in pediatric HCT that can decrease the risk of BO/BOS. Other aspects are the development of a new and more specific screening protocols and novels therapy that are able to improve the outcome significantly for those patients.

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