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Terapia FAM u dzieci z zarostowym zapaleniem oskrzelików po przeszczepieniu allogenicznych komórek krwiotwórczych

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FAM therapy in children with bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation

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Abstract

Introduction: Bronchiolitis obliterans syndrome (BOS) is one of the most frequent late-onset non-infectious pulmonary complications after allogeneic hematopoietic stem cell transplantation (allo-HSCT). It can lead to progressive respiratory insufficiency, and even death. BOS is a clinical term and does not necessarily require histological confirmation. A retrospective analysis of the clinical course in eight pediatric patients with BOS after allo-HSCT was performed.

Material and methods: The diagnosis of BOS was defined by the NIH-2014 criteria including pulmonary function tests and high resolution computer tomography scanning. Lung function score was simplified to forced expiratory volume in one second (FEV_1) values alone and symptoms score.

Results: FAM therapy (inhaled fluticasone, azithromycin and montelukast) was added to systemic immunosuppressive treatment typical for chronic graft-versus-host disease (cyclosporine, steroids) and continued after cessation of immunosuppressive therapy or was begun from the start as a separate treatment option. An improvement of lung function was observed in seven patients, while one patient deteriorated in FEV_1 test without clinical exacerbation.

Conclusion: Systemic corticosteroids remain the recommended first-line therapy for patients diagnosed with BOS in severe cases. Combination therapy with FAM may spare patients from systemic steroids and attenuate the need for prolonged systemic corticosteroid therapy.

Key words: allogeneic hematopoietic stem cell transplantation, non-infectious pulmonary complications, children

Introduction

Bronchiolitis obliterans syndrome (BOS) is one of the most common, non-infectious, late-onset respiratory complications after allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1]. The disease process leads to obturation and/or obliteration of the bronchioles, i.e. the final conductive airways in the respiratory system, up to 1–2 mm in diameter, through the inflammatory and fibrous tissue [2]. A pulmonary complication can present at any time, but in most cases does so within the first two years after transplantation, with various concomitant manifestations of chronic graft-versus-host disease (GvHD) in other organs. The prevalence of BOS in children is estimated at 3–6% [3]. The occurrence of pulmonary complications increases by several times the risk of transplantation-related death [4, 5]. Histopathological confirmation is difficult due to the low sensitivity of transbronchial biopsy and the potential complications of open lung biopsy. In 1993, the International Society for Heart and Lung Transplantation provided a clinical definition of BOS based on lung function, rather than histopathology criteria. Studies conducted over the next 20 years confirmed this thesis, and showed that there is no superiority of a histopathological examination over a diagnosis based on clinical symptoms, lung function tests and radiological examinations. Finally, in 2018, it was recognized that BOS is a clinical diagnosis based on functional tests without the need for histopathological confirmation [6, 7].

The multitude of potential causative factors indicates a multifactorial etiology of the disease, including drug-induced toxicity, radiation, opportunistic infection, and immunological reactions as well as individual susceptibility to the development of pulmonary complications, e.g. associated with respiratory efficiency before conditioning. Risk factors for the development of late pulmonary complications include methotrexate use for GvHD prophylaxis, hypogammaglobulinemia, history of acute GvHD, viral respiratory infections within the first 100 days after transplantation, conditioning with busulfan, transplantation of peripheral blood hematopoietic cells, and a history of interstitial pneumonia. Bronchiolitis obliterans affects mainly patients after allogeneic bone marrow transplantation; reports of the development of this disease after autologous transplantation are very rare [8].

Diagnosis of the disease is based on clinical symptoms, respiratory function tests and radiological examinations of the lungs using high resolution tomography. Clinical symptoms include cough, decreased exercise tolerance, and shortness of breath. The onset of the disease is often insidious, and clinical symptoms may only become apparent many years after a bone marrow transplant. High-resolution tomography shows airway damage in the form of thickening of the walls of bronchioles or widening of their lumen, or the presence of an air trap caused by segmental obstruction of the bronchioles [8].

In functional tests, BOS manifests as a new obstructive lung ventilation disorder. FEV_1 is recognized as the most reliable indicator of airway flow restriction and is considered to be a key parameter in the early detection of BOS. Patients with BOS may have an 'occult obstruction' on spirometry due to the early collapse of the bronchioles during forced expiration. This causes an underestimation of forced vital capacity (FVC), and consequently a false overestimation of the FEV_1/FVC obstruction index [9].

Treatment depends on the severity of the clinical course and the presence or absence of GvHD symptoms in other organs. Immunosuppressive treatment (cyclosporin, steroids), FAM regimen, and extracorporeal photopheresis (ECP) are the most commonly used.

The aim of this study was to assess the effectiveness of diagnostic and therapeutic procedures in pediatric patients undergoing allo-HSCT with late pulmonary complications in the form of bronchiolitis obliterans.

Material and methods

Study design

A retrospective analysis of the disease course and treatment results in pediatric patients after allo-HSCT with symptoms of lower respiratory tract disorders suggestive of BOS was performed. The patients underwent functional and imaging tests of the respiratory system, followed by appropriate treatment, and the effects of the adopted diagnostic and therapeutic procedures were assessed.

Patients

Study participants comprised pediatric patients after allo-HSCT performed between 2007 and 2022 at the Department of Bone Marrow Transplantation at the Antoni Jurasz University Hospital No. 1, *Collegium Medicum* in Bydgoszcz, Poland. Lung function tests, including spirometry and body plethysmography, were performed with MES LUNGTEST 1000 apparatus (MES, Kraków, Poland).

BOS diagnosis criteria

The adopted criteria for BOS diagnosis were based on pulmonary functional tests (PFTs) and high-resolution computed tomography (HRCT) according to the National Institutes of Health (NIH) (Table I). A BOS diagnosis requires meeting the listed spirometric criteria or showing functional progression (a decrease in FEV_1), ruling out an infection, and demonstrating the presence of an air trap in a radiological examination or body plethysmography [10].

Table I. Bronchiolitis obliterans syndrome (BOS) diagnostic criteria

I. Functional criteria — obstructive ventilatory disorders
1. FEV_1/FVC <5 percentile*
2. FEV_1 <75% predicted value with >10% decline in less than two years
II. Clinical criterion — ruling out respiratory infections
III. Confirmation of an air trap — presence of at least one of two BOS features
A. Presence of air trap in expiratory phase on HRCT or thickening of walls of small bronchi or presence of bronchiectasis
B. Presence of lung distension (‘air trap’) in functional tests: RV >120% of predicted value or RV/TLC ratio >95 percentile

*Normal range 5–95 percentile; FEV_1/FVC — forced expiratory volume in one second to forced vital capacity ratio; FEV_1 — forced expiratory volume in one second; HRCT — high-resolution computed tomography; RV — residual capacity; TLC — total lung capacity

The NIH criteria do not identify clinical conditions where there is a parallel decrease in FEV_1 and FVC with a normal FEV_1/FVC ratio. Such a spirometry pattern is common, and results from lung distension in the course of bronchiole disease due to BOS [11].

Disease severity criterion

FEV_1 has been established as a disease severity criterion [12], wherein the disease is classified as mild (FEV_1 >60%), or moderate (40–59%) or severe type (<39%).

Clinical evaluation of lung function

The updated National Institutes of Health criteria for clinical evaluation of chronic graft-versus-host disease (cGvHD) were used in this study. Lung Symptoms Score (LSS) included clinical symptoms (dyspnea) and spirometry (FEV_1 measurement) (Table II). When there was a discrepancy between stages, the parameter with the higher score was decisive [13].

Table II. Lung Symptoms Score

Score	**Clinical symptoms**	**FEV_1 [%]**
0	No shortness of breath	≥80
1	Mild degree: shortness of breath when climbing stairs	60–79
2	Moderate degree: shortness of breath when walking on flat ground	40–59
3	Severe degree: shortness of breath at rest, requires oxygen therapy	≤39

FEV_1 — forced expiratory volume in one second

Radiological examination

HRCT was performed in all patients at baseline and after treatment. Air trapping, wall thickening, and bronchiectasis were assessed.

BOS treatment

Recommendations [14] regarding monitoring and treatment of sudden lung function deterioration of obstructive type were adopted. In patients with FEV_1 >70% treatment with inhaled steroids was initiated, and in cases of a lower spirometric index or disease progression, systemic steroids were added. A FAM regimen was introduced additionally to systemic immunosuppressive treatment and continued during tapering and after discontinuation of immunosuppression, or was used as the only therapeutic option. The treatment scheme included oral administration of azithromycin at a dose of 5 mg/kg bw (max 250 mg) once a day, three days a week, for children 0-5 years; the anti-leukotriene drug (montelukast) at a dose of 5 mg for children 6–14 years and 10 mg for children >15 years once a day; and inhaled fluticasone propionate 250 μg twice a day for children 6–11 years, and 500 μg twice a day for children over 12 [15, 16].

Response to treatment

Response was assessed according to the PFTs criteria and clinical symptoms (NIH LSS) [13]:

- complete response (CR): normal FEV_1 after previously decreasing, score 0;
- partial response (PR): 10% increase in FEV_1, score decrease by 1 or more;
- progression: FEV_1 decrease by 10%, score increase by 1 or more except from 0 to 1.

Functional testing plan

Functional tests were performed at diagnosis, and then every 3–4 months until treatment discontinuation.

Results

Patient characteristics

Eight patients were included in analysis of symptoms, diagnosis and treatment of BOS after allo-HSCT. Clinical characteristics of patients according to risk factors for pulmonary complications after HSCT, including BOS, are set out in Table III.

Table III. Patient characteristics and risk factors for bronchiolitis obliterans syndrome (BOS)

BOS risk factor	**Patient**							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Age at time of transplantation [years]	17	6	6	6	8	8	3	14
Gender	M	F	M	M	M	F	F	F
Underlying disease	T-ALL-HR	ALL-HR, relapse after allo-HSCT (2015)	ALL-HR	AML	Transformation of MDS into AML	SAA	ALL — bone marrow relapse	ALL — second late bone marrow relapse
Transplantation type: 10/10 HLA-matched unrelated donor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Source of hematopoietic cells: peripheral blood	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conditioning with busulfan	No	Yes	Yes	Yes	Yes	No	No	No
Total body irradiation (TBI)	Yes	No	No	No	No	No	No	Yes
Infections within 100 days after transplantation	No	Yes (UTI, sepsis, CMV)	Yes (cystitis, BKV)	Yes (UTI, CMV, BOOP)	Yes (invasive pulmonary fungal disease)	Yes (pneumonia)	Yes (CMV, adenovirus, cystitis, BKV)	Yes (CMV, invasive pulmonary fungal disease, UTI)
Interstitial pneumonia	No	No	No	Yes	Yes	Yes	No	Yes
Hypogammaglobulinemia (substitution in months)	Yes (12)	No	Yes (6)	No	Yes (5)	Yes (19)	Yes (9)	Yes (10)
Acute GvHD	No	No	Yes (skin and intestine, stage II)	No	Yes (skin, stage I; intestine stage II)	Yes (skin, stage III; intestine, stage I)	Yes (skin and intestine, stage I)	Yes (skin, stage II)
Chronic GvHD in other organs	No	No	No	No	No	Yes (skin, oral cavity, genitourinary	No	Yes (skin, oral cavity, eye, GI,

						organs, eye, GI)		liver)
Methotrexate in prevention of GvHD	No	Yes	No	Yes	No	Yes	Yes	No

ALL-HR — acute lymphoblastic leukemia, high-risk group; allo-HSCT — allogeneic hematopoietic stem cell transplantation; AML — acute myeloblastic leukemia; BOOP — bronchiolitis obliterans organizing pneumonia; CMV — cytomegalovirus; GI — gastrointestinal; GvHD — graft-versus-host disease; HLA — human leukocyte antigen; MDS — myelodysplastic syndrome; SAA — severe aplastic anemia; T-ALL-HR — T-cell acute lymphoblastic leukemia, high-risk group; UTI — urinary tract infection

Analysis of clinical course

The symptoms and clinical course of BOS in the eight analyzed patients are set out in Table IV. In two cases, lung function abnormalities preceded radiological changes. In patients 3 and 4, the diagnosis of BOS was associated with a sharp decrease in FEV_1, respectively 26% within three months and 25% within two months.

Table IV. Signs and symptoms of bronchiolitis obliterans syndrome (BOS) in study group

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Signs	Dyspnea, decreased exercise tolerance	Decreased exercise tolerance			Cough	Cough	Decreased exercise tolerance	Decreased exercise tolerance
Symptoms	Tachypnea	Crackling, wheezing	None	None	Wheezing, bronchi	None	Crackling	None
Time since transplantation	54 days	13 months	38 months	54 months	17 months	9 months	8 years	11 months
Changes in HRCT	None	Yes	Yes	None	Yes	Yes	Yes	Yes

typical for BOS								

HRCT — high-resolution computed tomography

Obstructive ventilatory disorders were confirmed in 6/8 patients. The obturation reversibility test was negative and the obstruction was irreversible. Spirometry with concomitant decrease in FEV_1 and VC with normal FEV_1/VC ratio occurred in two patients. In these two, the reduced FEV_1 and VC parameters also did not meet the improvement criteria after the use of bronchodilators. Examinations in the body plethysmography cabin in seven patients showed features of an air trap. Mild BOS was found in four patients and moderate BOS in the other four. Patient 1 had an upgraded Lung Symptoms Score due to the severity of clinical symptoms (score 3 with FEV_1 = 42%) (Table V):

- vital capacity (VC) includes FVC or maximum vital capacity (VCmax), whichever is higher;
- in Patient 1, body plethysmography was not performed due to severe airway obstruction. After clinical improvement, he met an air trap functional criterion (RV >120%). A normal TLC value excludes restrictive changes in lung parenchyma.

Table V. Bronchiolitis obliterans syndrome diagnosis in analyzed patients

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
FEV_1/VC	<1 percentile	Normal but FEV_1 and VC <1 percentile	<1 percentile	3 percentile	<1 percentile	<1 percentile	<1 percentile	Normal but FEV_1 and VC <5 percentile
Obturation reversibility test	Negative	No improvement	Negative	Negative	Negative	Negative	Negative	No improvement
FEV_1	42% <1	71% <1	72% <1	65% <1	53% <1	74% <1	57% <1	65% <5

	percentile	percentile	percentile	percentile	percentile	percentile	percentile	percentile
RV >120%	Not tested	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Air trap in HRCT	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Thickening of bronchial walls	No	No	No	No	Yes	No	Yes	No
Bronchiectasis	No	No	No	No	No	No	Yes	No
Infection ruled out	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Histopathological confirmation	No	Yes	No	No	No	No	No	No
Ruling out of inflammatory infiltrates in X-ray	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
TLC	Not tested	Normal	>90 percentile	>90 percentile	Normal	>90 percentile	>90 percentile	>90 percentile
Lung Function Score	3	1	1	1	2	1	2	1

FEV_1 — forced expiratory volume in one second; FEV_1/VC — forced expiratory volume in one second to vital capacity ratio; RV — residual volume; HRCT — high-resolution computed tomography; TLC — total lung capacity

Therapy results

In the therapy of patients with BOS, the FAM regimen was used, either in combination with systemic steroid therapy (in five patients) or alone (in the other three) (Table VI). Four patients had a complete response, three patients had a partial response, and the other patient

progressed with deterioration of functional tests and simultaneous improvement of clinical ventilatory efficiency. Three patients were qualified for extracorporeal photopheresis (ECP) due to complications after systemic steroid therapy and the presence of chronic GvHD in other organs, while continuing the FAM regimen [17, 18]. Patient 2 was taking inhaled ciclesonide due to fluticasone intolerance. Due to the progression shown in the spirometric examination, she was qualified for further extracorporeal photopheresis procedures. The remaining patients are under clinical observation and undergoing control respiratory function tests.

Table VI. Therapeutic response in study group

Patient	**Duration of FAM treatment**	**Baseline FEV_1, LSS**	**Treatment discontinuation FEV_1, LSS**	**Response to treatment**
1	26 months	FEV_1 = 42%, score 3	FEV_1 = 63%, score 0	CR
2	33 months	FEV_1 = 64%, score 1	FEV_1 = 42%, score 0	Progression
3	14 months	FEV_1 = 72%, score 1	FEV_1 = 97%, score 0	CR
4	16 months	FEV_1 = 65%, score1	FEV_1 = 76%, score 0	CR
5	23 months	FEV_1 = 53%, score 2	FEV_1 = 48%, score 1	PR
6	14 months	FEV_1 = 74%, score 1	FEV_1 = 99%, score 0	CR
7	14 months	FEV_1 = 57%, score 2	FEV_1 = 55%, score1	PR
8	14 months	FEV_1 = 65%, score 1	FEV_1 = 74%, score 0	PR

FAM — inhaled fluticasone, azithromycin and montelukast; FEV_1 — forced expiratory volume in one second; LSS — Lung Symptoms Score; CR— complete response; PR — partial response

Discussion

The development of BOS is closely related to the presence of chronic GvHD in other organs, and according to some authors it is a manifestation of chronic GvHD in the lungs. Isolated BOS without symptoms of chronic GvHD in other organs is often observed in pediatric patients [19–21]. In the study group, chronic GvHD outside the respiratory system occurred in two patients. Early clinical signs include non-productive exercise-induced cough, decreased exercise tolerance, and wheezing. There is also a group of patients without clinical symptoms in the initial period in whom a decrease in lung function is detected in subsequent functional tests. In our patients, we performed functional tests after the occurrence of respiratory symptoms or chronic GvHD in other organs. Physical examination findings are nonspecific (diffuse crackles, wheezing) and may be absent despite NIH Lung Symptoms Score >0. In the study group, four patients had no signs with a score of 1.

The disease has differing clinical courses. It may manifest as a sudden deterioration of lung function with shortness of breath and a decrease in saturation. This situation occurred in 1/8 patients in the study group in the early post-transplant period (day 54). After completion of combination therapy, including continued FAM treatment for 26 months, this patient achieved a complete clinical response.

In some patients, there is a gradual decline in respiratory efficiency, although periodic exacerbations with long periods of stable lung function are also observed. Clinical symptoms and specific functional tests results may precede typical BOS-related radiological changes in HRCT, and therefore meeting the imaging tests criterion is not necessary in order to make a diagnosis. In the study group, two patients had no symptoms of BOS in lung tomography at the time of diagnosis. All patients met the spirometric criteria and presented clinical respiratory symptoms. Evaluation of lung function based on NIH LSS including only the signs and FEV_1 value in % correlates with survival rates [22]. Obturation, which increases over time, is a symptom of progressive bronchiole fibrosis and, ultimately, a decrease in vital capacity (VC). Revealing the deterioration of lung function in functional screening tests may contribute to the earlier detection of patients at risk of developing BOS after bone marrow transplantation.

The introduction of treatment according to the FAM framework in oligosymptomatic patients can limit the development of the disease and reduce the use of systemic steroids. In other cases, detection of progression via a spirometric test will allow for the swifter introduction of more intensive immunosuppressive treatment in order to stop the irreversible process of bronchiole fibrosis. According to published reports, the results of functional tests

(VC, FEV_1) correlate with survival rates in patients after allogeneic bone marrow transplantation [22, 23]. After the treatment, in seven of the eight patients receiving FAM therapy, improvement of lung function parameters was observed, including improvement of exercise tolerance and an increase in or a stabilization of the FEV_1 parameter in spirometry. The treatment was safe. No side effects were observed, but in one patient the inhaled drug was switched due to intolerance.

In conclusion, the FEV_1 parameter is the best recognized and most reliable indicator of airflow in the airways: its decrease indicates the severity of airflow obstruction. Performing follow-up spirometry tests in patients after bone marrow transplantation enables earlier identification of patients at risk of developing BOS. Earlier implementation of treatment increases the chance of stopping the fibrosis process and the decline in lung function [24].

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Authors' contributions

BT — sole author.

Conflict of interest

The author declares no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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