CHEST

Tamibarotene for the Treatment of Bronchiolitis Obliterans Associated With Chronic Graft-vs-Host Disease

Check for updates

Satoshi Watanabe, MD, PhD; Ken Ishiyama, MD, PhD; Keigo Saeki, MD; Noriyuki Ohkura, MD, PhD; Kazuo Kasahara, MD, PhD; and Shinji Nakao, MD, PhD

Bronchiolitis obliterans (BO) is a significant life-threatening complication that occurs after allogeneic hematopoietic stem cell transplantation (allo-HSCT), and it is associated with increased morbidity and mortality. BO responds poorly to corticosteroids or immunosuppressants, and there are currently no established treatment approaches. We herein describe a patient with biopsy-proven BO after allo-HSCT who was successfully treated with tamibarotene, a novel synthetic retinobenzoic acid. Tamibarotene led to a dramatic improvement in lung function as well as cutaneous manifestations of chronic graft-vs-host disease. A large prospective clinical trial is therefore warranted to confirm the efficacy of tamibarotene in BO.

CHEST 2019; 155(1):e1-e4

KEY WORDS: bronchiolitis obliterans; graft-vs-host disease; tamibarotene

Chronic graft-vs-host disease (cGVHD) is a life-threatening complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT) that remains a major cause of morbidity and mortality.[1] Bronchiolitis obliterans (BO), in particular, is the most detrimental posttransplantation pulmonary complication and is characterized by inflammation and fibroproliferative obliteration of the small airways, leading to progressive airflow obstruction.[2,3] There are currently no approved medications for the prevention or treatment of BO.[4] We herein report a patient with BO including cGVHD who was successfully treated with tamibarotene.

Case Report

A 47-year-old man with refractory acute promyelocytic leukemia (APL) presented to the respiratory disease department of our institution with oral mucositis, dermatitis, and shortness of breath. In 2012, the patient had received a diagnosis of APL and was initially treated by chemotherapy. He had achieved molecular remission and then received all-*trans* retinoic acid as maintenance therapy. However, because of several relapses of APL, he underwent allo-HSCT in February 2015 and October 2015. The calcineurin inhibitor tacrolimus was started in October 2015 for the prevention of GVHD. Regardless of the achievement of

ABBREVIATIONS: allo-HSCT = allogeneic hematopoietic stem cell transplantation; APL = acute promyelocytic leukemia; BO = bronchiolitis obliterans; cGVHD = chronic graft-vs-host disease

AFFILIATIONS: From the Department of Respiratory Medicine (Drs Watanabe, Saeki, Ohkura, and Kasahara) and the Department of Hematology (Drs Ishiyama and Nakao), Kanazawa University Hospital, Kanazawa, Ishikawa, Japan.

CORRESPONDENCE TO: Ken Ishiyama, MD, PhD, Department of Hematology, Kanazawa University Hospital, 13-1 Takara-machi, Kanazawa, Ishikawa, 920-8641, Japan; e-mail: ishiyama-knz@umin.ac.jp

Copyright © 2018 American College of Chest Physicians. Published by Elsevier Inc. All rights reserved.

DOI: https://doi.org/10.1016/j.chest.2018.08.1052

molecular remission after allo-HSCT, reverse transcriptase polymerase chain reaction for the *PML/RARA* fusion gene in a bone marrow specimen became positive in February 2016, indicating the molecular relapse of APL. To enhance graft-vs-leukemia effects, tacrolimus was tapered and stopped in April 2016. He also received tamibarotene as maintenance therapy in December 2015 and March 2016. In January 2017, one year after the second transplantation, he developed oral mucositis, dermatitis, and exertional dyspnea (Figs 1A, 1B). Pulmonary function tests revealed airway obstruction; results included the following: FVC, 3.70 L (94.6% predicted); FEV_1, 2.58 L (74.6% predicted); and FEV_1/FVC, 69.7%. His FEV_1 had markedly declined from 3.96 L (113.5% predicted) in June 2016 to 2.58 L (74.6% predicted) in January 2017. Inspiratory chest CT scan revealed bronchial thickness and bronchiectasis, and expiratory CT scan revealed slight mosaic perfusion. There were no other parenchymal abnormalities, such as infiltration, consolidation, or emphysema (Fig 1C). The sputum culture did not reveal any microorganisms, including mycobacteria and fungi. Cytomegalovirus antigen in his serum was negative. Reverse transcriptase polymerase chain reaction for the *PML/RARA* fusion gene was negative. These findings indicated that there was no evidence of infections and recurrence of APL. He was given inhaled corticosteroids, long-acting β_2-agonist, long-acting muscarinic antagonist, and leukotriene receptor antagonist in January 2017. However, 3 weeks after the treatment, his dyspnea and FEV_1 showed no improvement. An examination of a lung biopsy specimen obtained by video-assisted thoracoscopic surgery revealed pathological findings compatible with BO (Fig 1D). He therefore received a diagnosis of moderate cGVHD involving the mouth, skin, and lung. To keep his APL under control, tamibarotene at a dosage of 10 mg/d was started at the same time the diagnosis of cGVHD was made. He

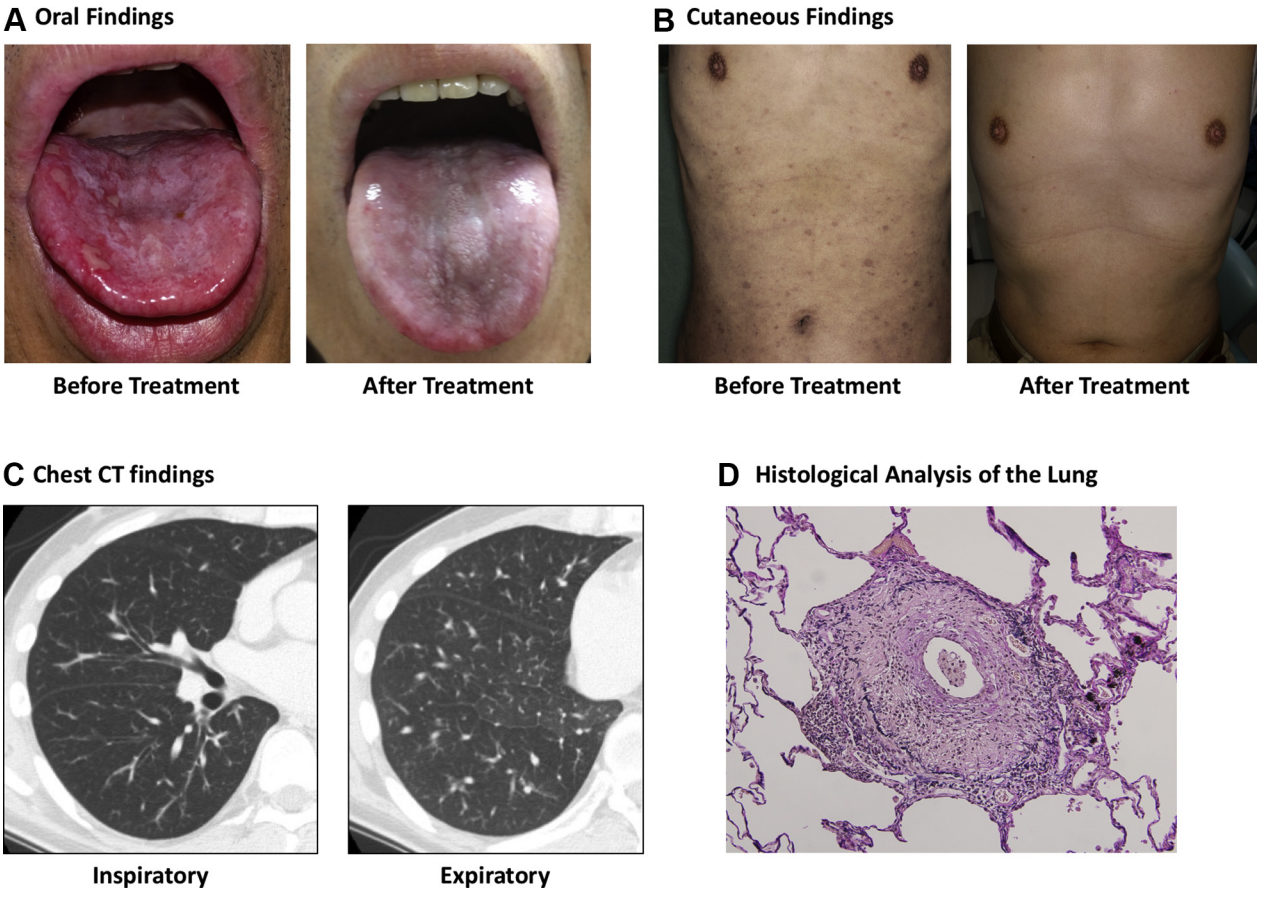

Figure 1 – *Mucocutaneous manifestations, chest CT scan findings, and lung biopsy specimen findings from the patient. A, Oral mucositis was visible on the tongue and the upper and lower lips before tamibarotene treatment. These were improved after treatment. B, The patient's body showed erythematous macules before treatment, which disappeared after treatment. C, Inspiratory chest CT scan revealed bronchial thickness and bronchiectasis, and expiratory CT scan revealed slight mosaic perfusion. D, Histologically, the lung biopsy specimen showed epithelial injury and fibroproliferative constriction of the bronchiole, consistent with bronchiolitis obliterans (Masson trichrome stain).*

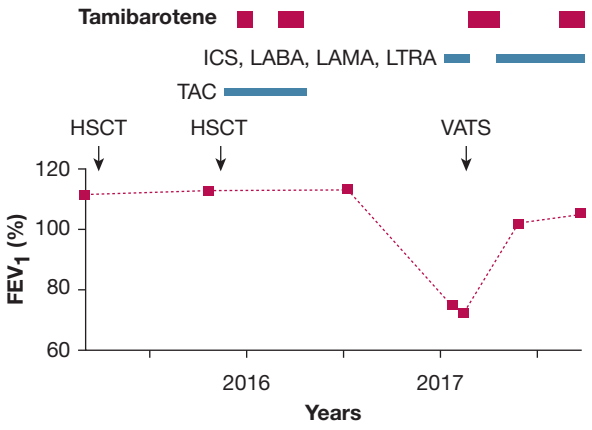

Figure 2 – *Time course of FEV_1 assessed before and after the start of tamibarotene administration. HSCT = hematopoietic stem cell transplantation; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; TAC = tacrolimus; VATS = video-assisted thoracoscopic surgery.*

received no other immunosuppressive therapies. Thereafter, his oral mucositis, dermatitis, and dyspnea all gradually improved (Figs 1A, 1B). Three months after treatment, his FEV_1 increased to 3.57 L (102.0% predicted) (Fig 2). Tamibarotene was continued for 8 weeks every 6 months. The patient has since been monitored for 1 year and has not developed any adverse events associated with tamibarotene.

Discussion

BO is a progressive and fatal lung disorder that is characterized by narrowing and obstruction of the bronchioles. The causes of BO include GVHD after allo-HSCT or lung transplantation, connective tissue diseases, infections, drugs, and inhaled chemicals. In particular, transplantation-related BO remains a major impediment to the long-term outcome, and it has been reported to be associated with an increased risk of death.[2] The therapeutic options for BO remain limited.[5] New, effective therapeutic strategies are therefore needed to achieve a better quality of life and long-term survival after HSCT.

The pathophysiology of BO following allo-HSCT is still not completely understood, but it is considered to be a part of the spectrum of manifestation of cGVHD. Classically helper T-cell type 1 (Th1)-mediated cell alloresponses are known to play a central role. Furthermore, previous studies have suggested the importance of Th17 cells for the development of prolonged immune activation and tissue fibrosis.[1,6]

Tamibarotene is a potent synthetic retinoid drug that has been approved for relapsed or refractory APL in Japan.[7,8] It also has a regulatory effect on the immune system and inflammatory responses that regulate both Th1 and Th17 responses as well as transforming growth factor-β expression, indicating the effective treatment for cGVHD.[9]

To the best of our knowledge, this is the first report of tamibarotene being clinically used in a patient with BO associated with cGVHD, which led to a dramatic improvement in lung function. There is only one clinical case that describes the efficacy of all-*trans* retinoic acid for cutaneous cGVHD.[10] However, compared with all-*trans* retinoic acid, tamibarotene has numerous advantages in that it is chemically more stable, has more potent activities, and fewer adverse events.[7] Furthermore, there are no available reports describing the efficacy of any other type of retinoid drug for BO.

Studies of combination therapies such as budesonide/formoterol, montelukast, and *N*-acetylcysteine,[11] and fluticasone, azithromycin, and montelukast[12] showed the benefit for BO after allo-HSCT. Although his dyspnea and FEV_1 apparently improved after starting tamibarotene, inhaled corticosteroids, bronchodilators, or leukotrienes receptor antagonist might also alleviate his symptoms. Prospective controlled trials of tamibarotene in patients with BO are thus warranted. If the efficacy is borne out in further study, the treatment could be applicable to other causes of BO such as that following lung transplantation.

Acknowledgments

Financial/nonfinancial disclosures: None declared.

References

1. Zeiser R, Blazar BR. Pathophysiology of chronic graft-vs-host disease and therapeutic targets. *N Engl J Med*. 2017;377(26):2565-2579.
2. Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. *N Engl J Med*. 2014;370(19):1820-1828.
3. Hildebrandt GC, Fazekas T, Lawitschka A, et al. Diagnosis and treatment of pulmonary chronic GVHD: report from the consensus conference on clinical practice in chronic GVHD. *Bone Marrow Transplant*. 2011;46(10):1283-1295.
4. Meyer KC, Raghu G, Verleden GM, et al. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur Respir J*. 2014;44(6):1479-1503.
5. Bergeron A, Chevret S, Granata A, et al. Effect of azithromycin on airflow decline-free survival after allogeneic hematopoietic stem cell transplant: the ALLOZITHRO randomized clinical trial. *JAMA*. 2017;318(6):557-566.
6. Yu Y, Wang D, Liu C, et al. Prevention of GVHD while sparing GVL effect by targeting Th1 and Th17 transcription factor T-bet and RORγt in mice. *Blood*. 2011;118(18):5011-5020.

7. Shinagawa K, Yanada M, Sakura T, et al. Tamibarotene as maintenance therapy for acute promyelocytic leukemia: results from a randomized controlled trial. *J Clin Oncol*. 2014;32(33):3729-3735.
8. Maeda Y, Nishimori H, Inamoto Y, et al. An open-labeled, multicenter phase II study of tamibarotene in patients with steroid-refractory chronic graft-versus-host disease. *Acta Med Okayama*. 2016;70(5):409-412.
9. Nishimori H, Maeda Y, Teshima T, et al. Synthetic retinoid Am80 ameliorates chronic graft-versus-host disease by down-regulating Th1 and Th17. *Blood*. 2012;119(1):285-295.
10. Gryn J, Crilley P. Tretinoin for the treatment of cutaneous graft-versus-host disease. *Bone Marrow Transplant*. 1990;5(4):279-280.
11. Kim SW, Rhee CK, Kim YJ, Lee S, Kim HJ, Lee JW. Therapeutic effect of budesonide/formoterol, montelukast and *N*-acetylcysteine for bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. *Respir Res*. 2016;17(1):63.
12. Williams KM, Cheng GS, Pusic I, et al. Fluticasone, azithromycin, and montelukast treatment for new-onset bronchiolitis obliterans syndrome after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2016;22(4):710-716.