Title	Effects of Azithromycin in bronchiolitis obliterans syndrome after hematopoietic SCTa randomized double-blinded placebo-controlled study
Author(s)	Lam, CLD; Lam, B; Wong, MKY; Lu, C; Au, WY; Tse, EWC; Leung, AYH; Kwong, YL; Liang, RHS; Lam, WK; Ip, MSM; Lie, AKW
Citation	Bone Marrow Transplantation, 2011, v. 46 n. 12, p. 1551-1556
Issued Date	2011
URL	http://hdl.handle.net/10722/139447
Rights	Creative Commons: Attribution 3.0 Hong Kong License

Effects of Azithromycin in bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation – a randomized double-blinded placebo-controlled study

David Chi-leung Lam, FRCP, PhD, Bing Lam, FRCP, Matthew KY Wong, MRCP, Crosby Lu, BSc, Wing-yan Au, MD, Eric Wai-choi Tse, FRCP, PhD, Anskar Yu-hung Leung, FRCP, PhD, Yok-lam Kwong, MD, Raymond Hin-suen Liang, MD, Wah Kit Lam, MD, Mary Sau-man Ip, MD, Albert Kwok-wai Lie, FRCP.

Department of Medicine, Queen Mary Hospital, University of Hong Kong

Running title: Azithromycin in bronchiolitis obliterans

Correspondence to:

Albert KW Lie

Division of Hematology, Medical Oncology and Hematopoietic Stem Cell Transplantation

Department of Medicine, Queen Mary Hospital, University of Hong Kong

102, Pokfulam Road

Hong Kong

Phone: (852) 22554400

Email: akwlie@hkucc.hku.hk

Research Support: This study and the drug used in this study were sponsored by Pfizer Pharmaceuticals.

Word counts: 1927

Keywords: Bronchiolitis obliterans syndrome (BOS), Azithromycin, hematopoietic stem cell transplantation (HSCT)

Abstract

Bronchiolitis obliterans syndrome(BOS) is an important complication after hematopoietic stem cell transplantation(HSCT). Recent observations suggested that azithromycin might improve lung function in BOS after HSCT. We conducted a randomized double-blinded placebo-controlled study on azithromycin in patients with BOS after HSCT. Treatment group(n = 10) received oral azithromycin 250mg daily while control group(n = 12) received placebo daily for 12 weeks. Respiratory symptoms were assessed by the St George Respiratory Questionnaires and spirometry at baseline(drug commencement), one month, two months, three months(drug cessation) and four months(one month after drug cessation). There was no significant difference in the baseline demographic characteristics between the treatment and the control group in age, gender, time from HSCT to BOS, time since diagnosis of BOS, chronic graft versus host disease(cGVHD), baseline respiratory symptom scores and baseline forced expiratory volume in one second(FEV_1). Throughout and after three months of treatment, there were no significant changes in respiratory symptom scores and FEV_1 measurements between the treatment and the control group. In conclusion, there was no significant benefit of three months of oral azithromycin on the respiratory symptoms and lung function in patients with relatively late BOS after HSCT in this randomized placebo-controlled study. (Abstract Word Count 195).

Introduction

Bronchiolitis obliterans syndrome (BOS) is an important pulmonary complication after hematopoietic stem cell transplantation (HSCT) for treatment of both acute and chronic leukemias as well as aplastic anemia (1). BOS usually develops as a late complication after HSCT (after the first 100 days post-transplantation) and is believed to be part of the chronic graft versus host disease (cGVHD) phenomenon (2-4). BOS can also occur after lung transplantation, in which case it is a manifestation of chronic graft rejection (5), although the underlying mechanism has not completely been identified (6).

BOS may be the result of immunologic injury targeting both endothelial and epithelial tissues in the pulmonary system, and such immunologic damage may represent cGVHD, or can be induced and aggravated by non-alloimmunologic inflammation associated with bacterial and viral infections (7), or silent chronic aspiration from gastro-esophageal reflux (8).

The mainstay of therapy for BOS after HSCT is treatment of chronic GVHD with augmentation of immunosuppression (9). Previous experience with BOS after lung transplantation has suggested a possible anti-inflammatory role for macrolides (10). Treatment with oral azithromycin for a median of ten months has been shown in various series of observational and retrospective studies in lung

transplant recipients with BOS to slow progression (11), and improve pulmonary function (12-14). However, a recent prospective study of maintenance azithromycin has shown no significant effects on the forced expiratory volume in one second (FEV_1) in lung transplant recipients with BOS (15). A beneficial effect of azithromycin on lung functions in BOS patients after HSCT has also been shown (16, 17). Therefore, the role of azithromycin in BOS after HSCT requires more rigorous appraisal.

Materials and methods

Patient recruitment criteria. Adult patients (> 18 years of age) who had undergone HSCT (allogeneic and autologous) at Queen Mary Hospital, Hong Kong, were eligible for inclusion. Patients with known allergy to macrolides or with other obvious reasons for pulmonary function decline such as infection or airway complications were excluded. Patients on long term macrolides were also excluded. The pulmonary function criteria for defining BOS were (i) FEV_1 < 75% predicted, with FEV_1/FVC ratio of < 0.70, and (ii) a reduction of FEV_1 by more than 10%, compared to the corresponding baseline values at time of HSCT, as modified from NIH criteria but air-trapping was not an inclusion criteria (7, 18). Spirometry parameters were measured with reference to Ip MS *et al* for the local Hong Kong subjects (19). Histopathological proof was required. The trial was registered with the Clinical Trial

Center, University of Hong Kong Hospital Authority Hong Kong West Cluster. Informed written consent was obtained from each patient before recruitment.

Study design. This was a randomized double-blinded placebo-controlled study. Recruited subjects were randomized to receive oral Azithromycin 250mg daily (Zithromax®, Pfizer) (treatment group) or placebo (one tablet daily) (Control group) for 12 weeks. All subjects received trial treatment in addition to their usual immunosuppressive regimen within the study period. Clinical assessments were done at baseline (drug commencement), 4 weeks, 8 weeks, 12 weeks (drug cessation) and 16 weeks (4 weeks after drug cessation) with spirometries and respiratory symptom assessment by the St George Respiratory Questionnaires (SGRQ)(20) at each visit. The SGRQ collected information on the subjects' respiratory symptoms, impact on physical functions and daily activities. The primary endpoint was respiratory symptoms as assessed by the SGRQ at four months. The secondary endpoint was spirometry parameters at four months. Additional spirometric assessments were performed at 6 and 12 months. The presence of chronic GVHD was recorded and severity graded according to the International Bone Marrow Transplant Registry (IBMTR) severity scoring (21) into mild, moderate and severe.

Statistical analyses. Comparisons between the treatment and placebo groups were made with respect to their demographic characteristics (age, gender, smoking history),

baseline spirometric parameters and percentage change at 3 months, and baseline St George Respiratory Questionnaire Scores (respiratory symptoms, impact of respiratory symptoms on daily life, activities and overall scores) and the score changes at 3 months. Student t tests and Mann Whitney U tests (non-parametric) were applied where appropriate. SPSS 15.0 was used for statistical calculations.

Results

Patients. From 1 April, 2006 to 30 December, 2007, 24 consecutive patients were recruited and randomized into either the treatment group (n = 12) or the placebo group (n = 12). There was no significant difference between the treatment and control group in terms of mean age (43.5 ± 8.6 vs 42.4 ± 9.2 years, p = 0.779), gender ratio, cGVHD grading (p = 0.410), mean Karnofsky performance score (p = 0.650), time from HSCT to inclusion (5.8 ± 4.0 vs 7.0 ± 3.3 years, p = 0.448) and time between BOS diagnosis to inclusion (4.3 ± 3.2 vs 5.8 ± 4.2 years, p = 0.359). Two patients from the treatment group withdrew from the study after recruitment and randomization. One of them complained of dyspepsia after taking 8 days of study drug and requested withdrawal from the study. The other patient, having taken 3 weeks of study drug, was admitted for pneumothorax, after which the patient withdrew from the study. Thus ten and twelve subjects completed the study in the treatment group and control group

respectively (Table 1).

Results. There was no significant difference in the baseline FEV_1 between the treatment and control group. There appeared to be worsening of lung function parameters in the treatment group compared with the control group, although the difference were not statistically significant (Table 2). There was also a consistent increase in the Respiratory Symptom scores but a consistent decrease in the Impact scores, Activities scores and Total scores in St George Respiratory Questionnaires (Table 3) assessment in the treatment group compared with the control group, although the difference was not statistically significant.

Discussion

This was the first randomized double-blinded placebo-controlled study on the effects of oral azithromycin on patients with BOS after HSCT.

The anti-inflammatory actions of azithromycin are thought to be mediated via action on neutrophils and cytokines especially interleukin-8 in early BOS in lung transplant recipients (22). Azithromycin also possesses antimicrobial actions against chlamydia and mycoplasma, although these may not be strong with the dosage of 250mg daily as used in the current study (23). It would be difficult to predict or ascertain whether azithromycin is acting through its anti-inflammatory actions on the

alloimmune system or its alternative mechanisms of action in BOS, as the underlying pathogenesis is not yet completely understood and these clinical studies on azithromycin were performed in lung transplant recipients (22, 23).

Although there were previous reports of favorable effects of azithromycin on the lung function of patients with BOS after HSCT (16) and lung transplantation recipients (24), similar favorable effects of azithromycin could not be demonstrated in our patients with BOS after HSCT in this study. This might reflect that the basic mechanisms underlying BOS in HSCT could be different from BOS after lung transplantation (2). In lung transplantation, BOS probably represents the direct rejection of donor organs (10); while in HSCT, BOS might represent part of the cGVHD, which could also involve the skin, gastrointestinal tract and liver (9). The risk factors for development of BOS after HSCT are also different from lung transplantation (25). The pathogenesis of post-transplant airflow obstruction after HSCT is hypothesized to be due to donor cytotoxic T lymphocytes targeting and attacking bronchiolar and other epithelial cells as part of cGVHD (9, 26) although this has not been confirmed in animal model or human subjects. However, the situation in lung transplant recipients was more clearly defined. There is augmentation of HLA class I and II antigens on lung endothelial and epithelial cells, and the involvement of recipient cytotoxic T lymphocyte in the airway via the release of proinflammatory

cytokines in the lung graft (27, 28). Another potential issue in post-transplant airflow obstruction is the presence of recurrent aspiration and unrecognized viral infection, both of which has been reported in lung transplantation (8), but similar possibility has not been documented in HSCT patients or in this study. Furthermore, BOS subjects in other studies (16) that reported benefits of azithromycin tended to be recruited immediately or soon after the diagnosis of BOS whereas in this study, the subjects recruited had BOS established for a few years, and this might account for the apparent non-responsiveness of patients to azithromycin. The fact that there was no significant improvement in respiratory symptoms and spirometry function may represent a therapeutic benefit of sustaining a stable state in BOS patients. However, this cannot be proven with this short term randomized-control trial.

During the study period, there was no significant change in the condition and immunosuppressant regimen. Also, there was no significant worsening in cGVHD profiles that warranted change of immunosuppressant regimen. However, the baseline cGVHD grades in the treatment group appeared to be slightly more severe than in the control group, although the difference was not statistically significant. This might contribute to the mild non-significant degree of worsening of lung function parameters and respiratory symptoms observed in the treatment group.

This study has a number of limitations. Only a relatively small number of

patients (22 BOS subjects) had been recruited, owing to the relative rarity of BOS as a post-HSCT complication. The diagnosis of BOS after HSCT is usually a clinical diagnosis based on symptoms and spirometric parameters (7). We would also like to emphasize that the study was done on late BOS patients, though we did not aim at selecting them for recruitment, which may make the condition very chronic and any changes in symptoms and lung functions slow to occur. The dosage of azithromycin (250mg daily for 12 weeks) used in this study, however, was different from the usual dose employed in clinical trials in lung transplant recipients and HSCT subjects (250mg 3 times per week for 12 weeks) (12, 16). Spirometry only was used as secondary endpoint measurement for this study, and lung volumes and diffusion factors were not measured. The presence of restriction may in turn affect the FEV_1 and FVC measurement. The previous use of bulsulphan in some of the recruited subjects could result in subsequent development of pulmonary toxicity with impaired diffusion capacity or combined restrictive component. However, subsequent followed up of all the subjects did not reveal clinical pulmonary toxicity and full lung function tests were not performed. Baseline CT Thorax and bronchoalveolar lavage were not performed as they were considered invasive investigation and underlying pulmonary infection resulting in lung function abnormality cannot be completely ruled out. We can only assumed that clinically significant pulmonary infection was not present as

subsequent follow up of these subjects up to one year after study did not show development of pulmonary infection. Histological proof for BOS was not available, mainly because of impaired lung function that made invasive procedures such as transbronchial biopsy or open lung biopsy unsafe in these subjects. Pathological diagnosis of BOS, if possible, could better characterize BOS in HSCT patients, and could allow better correlations of clinical response to therapeutics with therapeutics to be made. Three months of Azithromycin, however, could be too short for any BOS-related changes to occur. This small study should serve as the basis for a better balanced and multi-centered controlled study about this important issue.

Conclusion

We concluded that in this randomized placebo-controlled trial on azithromycin in patients with relatively late BOS after HSCT, no improvement of respiratory symptoms and lung function occurred after three months of treatment. Further studies with larger number of subjects, especially targeting the use of azithromycin in the early phase of BOS, may give more definitive results on its potential role in the treatment of BOS post-HSCT, which remains a rather refractory condition with substantial morbidity.

References

1. Soubani AO, Uberti JP. Bronchiolitis obliterans following haematopoietic stem cell transplantation. Eur Respir J. 2007 May;29(5):1007-19.
2. Dudek AZ, Mahaseth H. Hematopoietic stem cell transplant-related airflow obstruction. Curr Opin Oncol. 2006 Mar;18(2):115-9.
3. Watkins TR, Chien JW, Crawford SW. Graft versus host-associated pulmonary disease and other idiopathic pulmonary complications after hematopoietic stem cell transplant. Semin Respir Crit Care Med. 2005 Oct;26(5):482-9.
4. Williams KM, Chien JW, Gladwin MT, Pavletic SZ. Bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation. JAMA. 2009 Jul 15;302(3):306-14.
5. Verleden GM, Dupont LJ, Van Raemdonck DE. Is it bronchiolitis obliterans syndrome or is it chronic rejection: a reappraisal? Eur Respir J. 2005 Feb;25(2):221-4.
6. Grossman EJ, Shilling RA. Bronchiolitis obliterans in lung transplantation: the good, the bad, and the future. Transl Res. 2009 Apr;153(4):153-65.
7. Estenne M, Maurer JR, Boehler A, Egan JJ, Frost A, Hertz M, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transplant. 2002 Mar;21(3):297-310.
8. Hopkins PM, Aboyoun CL, Chhajed PN, Malouf MA, Plit ML, Rainer SP, et al. Association of minimal rejection in lung transplant recipients with obliterative bronchiolitis. Am J Respir Crit Care Med. 2004 Nov 1;170(9):1022-6.
9. Crawford SW, Clark JG. Bronchiolitis associated with bone marrow transplantation. Clin Chest Med. 1993 Dec;14(4):741-9.
10. Fietta AM, Meloni F. Lung transplantation: the role of azithromycin in the management of patients with bronchiolitis obliterans syndrome. Curr Med Chem. 2008;15(7):716-23.
11. Shitrit D, Bendayan D, Gidon S, Saute M, Bakal I, Kramer MR. Long-term azithromycin use for treatment of bronchiolitis obliterans syndrome in lung transplant recipients. J Heart Lung Transplant. 2005 Sep;24(9):1440-3.
12. Yates B, Murphy DM, Forrest IA, Ward C, Rutherford RM, Fisher AJ, et al. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. Am J Respir Crit Care Med. 2005 Sep 15;172(6):772-5.
13. Gerhardt SG, McDyer JF, Girgis RE, Conte JV, Yang SC, Orens JB. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: results of a pilot study. Am J Respir Crit Care Med. 2003 Jul 1;168(1):121-5.
14. Gottlieb J, Szangolies J, Koehnlein T, Golpon H, Simon A, Welte T. Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation.

Transplantation. 2008 Jan 15;85(1):36-41.
15. Porhownik NR, Batobara W, Kepron W, Unruh HW, Bshouty Z. Effect of maintenance azithromycin on established bronchiolitis obliterans syndrome in lung transplant patients. Can Respir J. 2008 May-Jun;15(4):199-202.
16. Khalid M, Al Saghir A, Saleemi S, Al Dammas S, Zeitouni M, Al Mobeireek A, et al. Azithromycin in bronchiolitis obliterans complicating bone marrow transplantation: a preliminary study. Eur Respir J. 2005 Mar;25(3):490-3.
17. Maimon N, Lipton JH, Chan CK, Marras TK. Macrolides in the treatment of bronchiolitis obliterans in allograft recipients. Bone Marrow Transplant. 2009 Jul;44(2):69-73.
18. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005 Dec;11(12):945-56.
19. Ip MS, Ko FW, Lau AC, Yu WC, Tang KS, Choo K, et al. Updated spirometric reference values for adult Chinese in Hong Kong and implications on clinical utilization. Chest. 2006 Feb;129(2):384-92.
20. Chan SL, Chan-Yeung MM, Ooi GC, Lam CL, Cheung TF, Lam WK, et al. Validation of the Hong Kong Chinese version of the St. George Respiratory Questionnaire in patients with bronchiectasis. Chest. 2002 Dec;122(6):2030-7.
21. Lee SJ, Klein JP, Barrett AJ, Ringden O, Antin JH, Cahn JY, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. Blood. 2002 Jul 15;100(2):406-14.
22. Verleden GM, Vanaudenaerde BM, Dupont LJ, Van Raemdonck DE. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. Am J Respir Crit Care Med. 2006 Sep 1;174(5):566-70.
23. Schultz MJ. Macrolide activities beyond their antimicrobial effects: macrolides in diffuse panbronchiolitis and cystic fibrosis. J Antimicrob Chemother. 2004 Jul;54(1):21-8.
24. Verleden GM, Dupont LJ. Azithromycin therapy for patients with bronchiolitis obliterans syndrome after lung transplantation. Transplantation. 2004 May 15;77(9):1465-7.
25. Santo Tomas LH, Loberiza FR, Jr., Klein JP, Layde PM, Lipchik RJ, Rizzo JD, et al. Risk factors for bronchiolitis obliterans in allogeneic hematopoietic stem-cell transplantation for leukemia. Chest. 2005 Jul;128(1):153-61.
26. O'Brien KD, Hackman RC, Sale GE, Prentice R, Deeg J, Thomas ED, et al. Lymphocytic bronchitis unrelated to acute graft-versus-host disease in canine marrow

graft recipients. Transplantation. 1984 Mar;37(3):233-8.
27. Taylor PM, Rose ML, Yacoub MH. Expression of MHC antigens in normal human lungs and transplanted lungs with obliterative bronchiolitis. Transplantation. 1989 Sep;48(3):506-10.
28. Hodge G, Hodge S, Chambers D, Reynolds PN, Holmes M. Bronchiolitis obliterans syndrome is associated with absence of suppression of peripheral blood Th1 proinflammatory cytokines. Transplantation. 2009 Jul 27;88(2):211-8.

Table 1 Characteristics of recruited subjects

Patients	Gender	Age	Smoking habit	Pre-BMT Diagnosis	Pre-transplant therapy	Conditioning regimen	Time from HSCT to BO (days)	Pre-existing respiratory diseases	Respiratory diseases developed after HSCT	Degree of HLA matching	Donor relationship	KPS	Wt loss	Gut cGVHD	Skin cGVHD	Oral mucosa cGVHD	Baseline FEV_1 (Liter)	End of study FEV_1 (Liter)	Current medication
A-1	F	46	NS	CML	Hydroxyurea	Bu-Cy	502			6	Sib	≧80	No	No	NA	NA	2.15	2.12	Seretide, Rhinocort
A-2	F	31	NS	DLBC Lymphoma (transformed to MDS)	CEOP; DHAP	Big Bu-Cy	177	Rt pneunothorax with surgical pleurodesis 3/2006		8	UD	≧80	Yes	No	NA	NA	1.01	NA	CSP/Pulmicort/Seretide
A-3	F	44	NS	CML	Hydroxyurea	Bu-Cy	104		Bronchiectasis	6	Sib	≧80	Yes	No	NA	NA	0.94	0.84	Serevent/Fluticasone Progionate/IVIG
A-4	M	52	NS	AML	3:7 (Idarubicin+Cytarabine); AraC+Mitoxantrone	Bu-Cy	1391			6	Sib	≧80	No	No	NA	NA	1.21	1.27	Seretide/CSP/MMF
A-5	F	34	NS	CML	Hydroxyurea; Interferon; Glivec	Fludarabine-TBI	475			7	UD	≧80	Yes	Yes	NA	NA	0.6	0.61	CSP/MMF/IVIG
A-6	M	45	NS	NHL	R-CEOP; DHAP; IMVP; MiniBEAM	Cy-TBI	349			5	Sib	≧80	Yes	Yes	NA	NA	2.3	2.15	CSP/MMF/Pulmicort
A-7	M	56	EX	MDS	None	Fludarabine-TBI	806		Interstitial lung disease	6	Sib	≧80	Yes	No	NA	NA	1.65	1.58	Cyclophosphamide; Prednisolone
A-8	M	35	EX	Myelofibrosis	3:7 (Idarubicin+Cytarabine)	Bu-Cy	549			6	Sib	≧80	Yes	Yes	NA	NA	1.6	1.91	CSP
A-9	F	57	NS	CML	Hydroxyurea	Bu-Cy	456	Bronchiectasis		6	Sib	≧80	Yes	No	NA	NA	0.99	NA	Seretide/Ventolin
A-10	M	31	EX	SAA	Methylprednisolone; Cyclosporin A; Antithymocyte Globulin	Cy-ATG	662			6	Sib	<80	Yes	No	Yes	Yes	1.46	1.55	FK506
A-11	M	39	NS	CML	Hydroxyurea	Bu-Cy	260		Bronchiectasis	6	Sib	≧80	No	No	NA	NA	1.73	1.87	Seretide/Ventolin
A-12	M	53	EX	AML	7:3 (Cytarabine+Daunorubicin); 5:2 (Etoposide+Daunorubicin)	Bu-Cy	500		Bronchiectasis	6	Sib	≧80	No	No	NA	NA	0.71	0.5	CSP/MMF/Prednislone/Ventolin/Seretide
P-13	M	38	NS	CML	Hydroxyurea	Bu-Cy	600			6	Sib	≧80	Yes	No	NA	NA	1.96	2.51	Seretide
P-14	F	37	NS	CML	Hydroxyurea	Bu-Cy	122		Bronchiectasis	6	Sib	≧80	No	No	NA	NA	0.98	1.07	Seretide
P-15	M	45	EX	MDS	None	Bu-Cy	318		Bronchiectasis	6	Sib	<80	Yes	No	No	Yes	0.71	0.71	Symbicort/Ventolin/Theophylline/IVIG
P-16	M	34	NS	CML	Hydroxyurea	Bu-Cy	303		asthma	6	Sib	≧80	No	No	NA	NA	1.96	1.78	Pulmicort
P-17	M	46	NS	CML	Hydroxyurea	Bu-Cy	150			6	Sib	≧80	No	No	NA	NA	2.6	2.57	Pulmicort/Ventolin
P-18	M	57	EX	MM	VAD	Fludarabine-TBI	822			6	Sib	≧80	Yes	No	NA	NA	1.32	1.25	None
P-19	F	48	NS	AML	7:3 (Cytarabine+Daunorubicin); 5:2 (Etoposide+Daunorubicin); Cytarabine	Fludarabine-TBI	701			6	Sib	≧80	Yes	Yes	NA	NA	0.64	0.64	CSP/MMF/IVIG/Seretide
P-20	M	44	NS	CML	Hydroxyurea	Bu-Cy	214			6	Sib	≧80	No	No	NA	NA	1.58	1.57	Seretide
P-21	M	38	NS	AML	7:3 (Cytarabine+Daunorubicin); Cytarabine+Thioguanine; Cytarabine+Mitoxantrone	Bu-Cy-TBI	420		asthma	6	Sib	≧80	No	No	NA	NA	1.69	1.59	Seretide/Ventolin
P-22	F	42	NS	AML	7:3 (Cytarabine+Daunorubicin)	ICE	1093			6	Sib	<80	Yes	No	Yes	Yes	1.01	0.96	Seretide/Ventolin/CSP/IVIG/MMF
P-23	M	56	EX	DLBC Lymphoma	CVP; NOPP	Cy-TBI	152	pneumothorax/COPD		7	UD	≧80	No	No	NA	NA	2.12	2.34	MMF/IVIG/Ventolin/Pulmicort
P-24	M	24	EX	CML	Hydroxyurea	Bu-Cy	262		Right pneumothorax with surgical pleurodesis; Bronchiectasis	6	Sib	≧80	No	No	NA	NA	1.64	1.45	Pulmicort

Patients with code starting with ‘A-‘ were in the treatment group, those with ‘P-‘ were in the Placebo group

M = males, F = females; NS = non-smoker, EX = ex-smoker; CML = chronic myeloid leukemia, DLBC = Diffuse large B cell lymphoma, AML = acute myeloid leukemia, NHL = non-Hodgkin’s lymphoma, MDS = myelodysplastic syndrome, SAA = severe aplastic anemia; BMT = bone

marrow transplantation, BO = bronchiolitis obliterans; CT = computed tomography; KPS = Karnofsky Performance Score; Wt loss = weight loss; NA = presentation so minor that it was regarded as absent

Bu = Busulphan, Cy = Cyclophosphamide, TBI = Total body irradiation; Degree of HLA-matching: 6 Antigen Matching with HLA-A, -B and –DR for matched sibling; up to 8 Antigen Matching with HLA-A, -B, -C and –DR for unrelated donor; Sib = matched sibling, UD = unrelated donor; CSP = cyclosporine, IVIG = intravenous immunoglobulin, MMF = mycophenolate mofetil, FK506 = Tacrolimus.

CEOP = Cyclophosphamide+Epirubicin+Vincristine+Prednisolone;

DHAP = Cisplatin+Cytarabine+Dexamethasone;

R-CEOP = Mabthera+Cyclophosphamide+Epirubicin+Vincristine+Prednisolone;

IMVP = Ifosfamide+Methotrexate+Etoposide;

MiniBEAM = Carmustine+Etoposide+Cytarabine+Melphalan;

VAD = Vincristine+Adriamycin+Dexamethasone;

CVP = Cyclophosphamide+Vincristine+Prednisolone;

NOPP = Mitoxantrone+Vincristine+Procarbazine+Prednisolone

Table 2 Comparisons of baseline spirometric parameters and changes after treatment between the treatment group and the control group

	Treatment	**Control**	**Significance**
Baseline Mean FEV_1 (L)	1.44 ± 0.57	1.52 ± 0.60	0.746
Mean FEV_1 (L)			
At 1 month	1.43 ± 0.59	1.48 ± 0.61	0.860
At 2 month	1.41 ± 0.64	1.53 ± 0.67	0.650
At 3 month	1.43 ± 0.58	1.62 ± 0.72	0.510
At 4 month	1.44 ± 0.61	1.54 ± 0.66	0.726
Mean FEV_1 % change			
At 1 month	- 0.67 ± 8.78	- 2.14 ± 12.15	0.751
At 2 month	- 3.41 ± 14.02	+ 0.95 ± 13.72	0.473
At 3 month	- 0.47 ± 13.57	+ 6.11 ± 15.02	0.293
At 4 month	- 1.21 ± 13.09	+ 0.74 ± 10.79	0.711
Baseline Mean FVC (L)	2.86 ± 0.67	3.07 ± 0.86	0.525
Mean FVC (L)			
At 1 month	2.83 ± 0.71	3.11 ± 0.89	0.403
At 2 month	2.89 ± 0.68	3.03 ± 0.91	0.674
At 3 month	2.91 ± 0.72	3.12 ± 0.92	0.554
At 4 month	2.94 ± 0.74	3.05 ± 0.86	0.757
Mean FVC % change			
At 1 month	- 1.27 ± 7.97	1.97 ± 8.49	0.369

At 2 month	1.13 ± 8.40	- 1.34 ± 6.70	0.462
At 3 month	1.73 ± 10.0	1.61 ± 7.23	0.974
At 4 month	2.79 ± 8.88	- 0.37 ± 5.62	0.345
Baseline Mean $FEF_{25-75\%}$	1.56 ± 3.13	0.68 ± 0.52	0.402
Mean $FEF_{25-75\%}$ (L)			
At 1 month	0.61 ± 0.43	0.65 ± 0.40	0.804
At 2 month	0.64 ± 0.45	0.78 ± 0.77	0.583
At 3 month	0.61 ± 0.38	0.85 ± 0.92	0.424
At 4 month	0.60 ± 0.34	0.72 ± 0.59	0.576
Mean $FEF_{25-75\%}$ % change			
At 1 month	- 19.79 ± 44.35	+ 13.92 ± 54.79	0.126
At 2 month	- 40.32 ± 129.20	+ 5.85 ± 20.55	0.291
At 3 month	- 6.30 ± 34.08	+ 22.85 ± 46.13	0.105
At 4 month	- 9.11 ± 33.17	+ 9.20 ± 26.85	0.178

Table 3 Comparisons of St George Respiratory Questionnaire Scores between the treatment group and the control group

	Treatment	**Control**	**Significance**
Symptom scores (baseline)	56.2 ± 30.8	57.1 ± 18.1	0.223
% change in symptom scores			
At 1 month	+ 2.1 ± 10.6	+ 3.0 ± 18.0	0.582
At 2 month	+ 0.6 ± 7.0	- 0.1 ± 14.5	0.821
At 3 month	+ 2.3 ± 15.4	- 5.6 ± 16.8	0.711
At 4 month	+ 4.2 ± 25.5	+ 0.7 ± 10.8	0.628
Impact scores (baseline)	37.2 ± 21.0	32.0 ± 24.2	0.113
% change in Impact scores			
At 1 month	- 14.9 ± 29.5	- 3.5 ± 34.8	0.539
At 2 month	- 12.6 ± 31.5	+ 1.4 ± 47.2	0.722
At 3 month	- 11.1 ± 46.6	- 6.2 ± 42.9	0.923
At 4 month	- 18.6 ± 39.9	+ 21.0 ± 75.5	0.283
Activity scores (baseline)	56.8 ± 25.2	44.8 ± 22.4	0.125
% change in Activity scores			
At 1 month	- 10.9 ± 21.0	+ 2.8 ± 17.2	0.582
At 2 month	- 5.3 ± 23.6	+ 16.6 ± 49.8	0.821
At 3 month	- 7.3 ± 26.0	+ 25.0 ± 65.9	0.283

At 4 month	- 17.0 ± 37.4	+ 21.0 ± 78.6	0.093
Total scores (baseline)	46.3 ± 19.5	40.0 ± 20.2	0.542
% change in Total scores			
At 1 month	- 10.8 ± 20.5	-0.2 ± 17.3	0.381
At 2 month	- 7.3 ± 22.7	+ 5.1 ± 31.5	0.923
At 3 month	- 8.8 ± 30.0	+ 1.3 ± 23.9	0.628
At 4 month	- 14.6 ± 32.8	+ 7.6 ± 40.5	0.314