Dynamic evaluation of the correlativity between CD4 cell percentage and FEV1 can predict the balance of the state of the immune system in pulmonary graft versus host disease patients

Ting Zhou[1,2], Lixin Xie[1]

[1]Department of Respiratory, First Medical Center, PLA General Hospital, Beijing 100853, China; [2]School of Medicine, Nankai University, Tianjin 300071, China

Correspondence to: Lixin Xie. Department of Respiratory, First Medical Center, PLA General Hospital, Haidian district, Beijing 100853, China. Email: laoxie301@126.com.

Abstract: Pulmonary graft versus host disease (GVHD) features irreversible airflow obstruction, which treatment typically involves immunosuppressive regimens. Regardless of whether GVHD is caused by immune overreaction or infection caused by immunologic suppression, the end result is death. Therefore, it is crucial to maintain a balance. We assessed 15 patients after hematopoietic stem cell transplantation (HSCT) in our hospital and collected CD4 cell percentage, forced expiratory volume in 1 s (FEV1) and FEV1/forced vital capacity (FVC) data from the same period. Here, we present a dynamic evaluation of the correlativity between the CD4 cell percentage and FEV1 that can predict state balance in pulmonary GVHD patients.

Keywords: Hematopoietic stem-cell transplantation; CD4 cell percentage; pulmonary function; immune

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective therapy for many hematologic non-malignancies or malignancies (1). In long-term follow-up after transplantation, graft versus host disease (GVHD) remains a major cause of non-relapse mortality. Approximately 50% of SCT recipients develop GVHD. Pulmonary GVHD features irreversible airflow obstruction, which treatment typically involves immunosuppressive regimens. Regardless of whether GVHD caused by immune overreaction or infection caused by immunologic suppression, the end result is death. Therefore, it is crucial to maintain a balance. The CD4 cell percentage can reflect the state of the immune system, whereas FEV1 (% predicted) and FEV1/FVC (actual) can be used to assess the degree of airway obstruction. Here, we present a dynamic evaluation of the correlativity between the CD4 cell percentage and FEV1 that can predict state balance in pulmonary GVHD patients.

We assessed 15 patients (*Table 1* shows clinical characteristics of 15 patients) after HSCT in our hospital and collected CD4 cell percentage, FEV1 and FEV1/FVC data from the same period (*Table 2*) (The same period was considered less than 20 days between the pulmonary function assessment and the CD4 cell percentage). We plotted these data in scatter plots, which reveal that FEV1 (% predicted) or FEV1/FVC is increased, whereas the CD4 cell percentage is reduced. An analysis of FEV1 (% predicted) and CD4 cell percentage was performed using a bivariate correlation test, and the Pearson correlation coefficient (r) was –0.704 (P=0.000). The relevant FEV1/FVC and CD4 cell percentage values reveal a common conclusion (r=–0.747, P=0.000) Then, we divided the data into two groups according to the CD4 cell percentage. In GROUP 1, CD4 cell percentages were less than 0.25, whereas GROUP 2 included values greater than or equal to 0.25. Comparisons of FEV1 and FEV/FVC between

Table 1 Clinical characteristics of 15 patients

Patient	Age/sex	Primary disease	Conditioning regimen	Type of HSCT	HLA disparity	Sex disparity	Date of HSCT
1	40/M	MDS-RAEB	Improved BU/CY + ATG	RBMT	Partially matched	Mismatched	2012.3.29
2	33/M	AML-M2	–	RBMT	Matched	–	2009
3	51/M	AML-M2a	BU/CY + ATG	RBMT	Partially matched	Mismatched	2015.12.21
4	23/M	AML-M2	Improved BU/CY	RBMT	Matched	Mismatched	2015.5.8
5	51/M	MDS-RAEB-II	Improved BU/CY	RBMT	Matched	Mismatched	2015.6.10
6	24/M	AML-M2	BU/CY + ATG	RBMT	Partially matched	Mismatched	2017.1.9
7	35/F	AML-M2	Improved BU/CY + ATG	RBMT	Haploidentical	Matched	2015.10.15
8	47/F	AML-M4	Improved BU/CY	RBMT	Matched	Matched	2015.3.30
9	37/M	NHL	Improved BU/CY + ATG	RBMT	Partially matched	Mismatched	2016.6.2
10	40/F	AML-M2a	Improved BU/CY	RBMT	Matched	Matched	2016.8.22
11	42/F	ALL-Ph+	Improved BU/CY	RBMT	Matched	Mismatched	2017.4.6
12	46/M	AML	Improved BU/CY + ATG	RBMT	Matched	Mismatched	2016.8.29
13	42/M	NHL	BU/CY + ATG	RBMT	Haploidentical	Matched	2018.2.13
14	29/F	AML-M2	Improved BU/CY + ATG	RBMT	Haploidentical	Matched	2016.3.28
15	35/M	MDS-RAEB-II	Improved BU/CY	RBMT	Matched	Matched	2015.4.20

HSCT, hematopoietic stem cell transplantation; HLA, human leukocyte antigen; MDS, myelodysplasia; RAEB, refractory anemia with excess of blasts; BU, busulfan; CY, cyclophosphamide; ATG, antithymocyte globulin; RBMT, related bone marrow transplantation; AML, acute myeloid leukemia; NHL, non-Hodgkin lymphoma; ALL, acute lymphoblastic leukemia.

the two groups were both performed using an independent sample t-test. FEV1 in GROUP 1 is increased compared with GROUP 2 (P=0.000). In addition, FEV1/FVC in GROUP 1 is increased compared with FEV1 in GROUP 2 (P=0.000).

Pulmonary GVHD features irreversible airflow obstruction and typically occurs within the first 2 years after allo-HSCT. The typical pulmonary function phenotype is characterized as follows: forced expiratory volume in 1 s (FEV1) <70% and FEV1/forced vital capacity (FVC) ratio <0.7. FEV1 and FEV1/FVC are negatively correlated with the severity of pulmonary GVHD. The pathophysiology of GVHD has generally proven to be autoimmune. Furthermore, increasing evidence suggests that GVHD is caused by donor T lymphocytes attacking recipient cells, resulting in immune-mediated tissue damage (2). Numerous experiments have demonstrated that alloreactive T cells move into the thymus and damage medullary thymic epithelial cells (mTECs), resulting in the production of autoreactive CD4 T cells. Autoreactive CD4 T cells are also derived from CD4 T cells in transplants probably through recognizing nonpolymorphic antigens (3-5). Autoreactive T cells interact with donor-derived DCs and B cells, resulting in mutual expansion, autoantibody production and GVHD development (6). During the process, CD4 T cells play an important role, causing GVHD through either thymic-dependent or thymic-independent mechanisms. CD4 cells are mainly involved in humoral immunity with antibody release and represent a potential mechanism leading to inflammation, epithelial destruction, pulmonary fibrosis, and air trapping (7-9). Available evidence indicates that CD4 helper T cells play an important role in the initiation and regulation of GVHD.

Our report demonstrates that the CD4 cell percentage is closely associated with pulmonary function in GVHD patients after HSCT. The results demonstrate that pulmonary function can remain in a better condition when the CD4 cell percentage is less than 0.25. Patients are easily infected when the CD4 cell percentage is extremely low due to excessive immunosuppression. Therefore, lower CD4 cell percentages are not safer. CD4 cell percentages equal to 0.25 offer the most benefits to patients.

Table 2 CD4 cell percentage, FEV1 and FEV1/FVC of the 15 patients

Group	Patient	CD4[†]	FEV1 (% predicted)[‡]	FEV1/FVC (actual)[‡]	Days[§]
1	3	0.11	101.80%	84.86%	20
	4	0.18	85.30%	91.87%	3
	5	0.24	92.40%	86.42%	2
		0.16	99.40%	87.16%	3
	6	0.17	108.40%	89.88%	0
		0.16	109.40%	89.09%	2
	7	0.11	86.70%	81.14%	15
		0.16	83.90%	78.06%	1
	9	0.15	85.20%	95.25%	0
		0.16	87.50%	96.82%	2
	11	0.08	87.00%	89.39%	3
	12	0.20	73.20%	72.16%	1
	13	0.03	71.10%	83.96%	0
	14	0.18	81.50%	112.00%	1
	15	0.17	61.10%	68.79%	2
2	1	0.37	46.30%	50.11%	0
		0.39	37.10%	46.01%	1
		0.31	38.10%	46.09%	4
	2	0.30	13.90%	31.44%	1
	8	0.31	37.40%	39.20%	1
		0.35	57.00%	48.98%	10
	10	0.37	61.10%	67.69%	15
		0.25	60.70%	67.68%	15

[†], the CD4 cell percentage was assessed using the BD machine by flow cytometry; [‡], pulmonary function tests (PFTs) were performed within the clinical pulmonary function laboratories of participating institutions according to institutional practice. Lung function was assessed by whole-body plethysmography using the YEGE machine; [§], the number of days between the pulmonary function and the CD4 cell percentage. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

References

1. Hu N, Cheng Z, Pang Y, et al. Prognostic effect of allogeneic hematopoietic stem cell transplantation on first and non-first complete remission in acute myeloid leukemia. Ann Transl Med 2019;7:500.
2. Grønningsæter IS, Tsykunova G, Lilleeng K, et al. Bronchiolitis obliterans syndrome in adults after allogeneic stem cell transplantation-pathophysiology, diagnostics and treatment. Expert Rev Clin Immunol 2017;13:553-69.
3. Zhao D, Young JS, Chen YH, et al. Alloimmune Response Results in Expansion of Autoreactive Donor CD4 T Cells in Transplants That Can Mediate Chronic Graft-versus-Host Disease. J Immunol 2011;186:856-68.
4. Rangarajan H, Yassai M, Subramanian H, et al. Emergence of T cells that recognize nonpolymorphic antigens during graft-versus-host disease. Blood 2012;119:6354-64.
5. Young JS, Wu T, Chen Y, et al. Donor B Cells in Transplants Augment Clonal Expansion and Survival of Pathogenic CD4 T Cells That Mediate Autoimmune-like Chronic Graft-versus-Host Disease. J Immunol 2012;189:222-33.
6. Wu T, Young JS, Johnston H, et al. Thymic Damage, Impaired Negative Selection, and Development of Chronic Graft-versus-Host Disease Caused by Donor CD4 and CD8 T Cells. J Immunol 2013;191:488-99.
7. Hostettler KE, Halter JP, Gerull S, et al. Calcineurin inhibitors in bronchiolitis obliterans syndrome following stem cell transplantation. Eur Respir J 2014;43:221-32.
8. Fukami N, Ramachandran S, Saini D, et al. Antibodies to MHC Class I Induce Autoimmunity: Role in the Pathogenesis of Chronic Rejection. J Immunol 2009;182:309-18.
9. Williams KM, Chien JW, Gladwin MT, et al. Bronchiolitis Obliterans After Allogeneic Hematopoietic Stem Cell Transplantation. JAMA 2009;302:306-14.