Non-infectious pulmonary complications such as chronic airflow obstruction, bronchiolitis obliterans organizing pneumonia, radiation- and drug-induced lung injuries, diffuse pulmonary hemorrhage, and transfusion-related lung injury are well recognized in leukemia patients who receive high-dose chemotherapy and supported with hematopoietic stem cell transplantation (HSCT).\(^1,2\) These complications may cause transient or permanent damage to the lung parenchyma and pulmonary function changes in patients who achieve long-term survival. The frequently-encountered pulmonary function changes of non-infectious pulmonary complications after HSCT include obstructive ventilatory defects, restrictive ventilatory defects, obstructive ventilatory defects with reduced forced vital capacity (FVC), mixed obstructive and restrictive ventilatory defects, and reduction in the diffusing capacity of the lung for carbon monoxide (DLCO).\(^1,2\)

For adoption of preventive or therapeutic measures for those possible pulmonary complications after HSCT, transplantation oncologists in many institutes routinely perform pulmonary function studies for stem cell recipients before and after HSCT even though their predictive value and clinical usefulness are in doubt.\(^3\) Pulmonary function studies encompass spirometry as well as determination of lung volumes and diffusion capacity.\(^4–7\) Spirometry measures the rate of air exhaled or inhaled as a function of time.\(^4\) The FVC, forced expiratory volume in the first second (FEV\(_1\)), and the FEV\(_1\)/FVC ratio are the most commonly reported values. The disproportionate reduction in FEV\(_1\)/FVC to below the lower normal limit indicates an obstructive ventilatory change. The FEV\(_1\) is further used to determine the severity of the obstruction. Total lung capacity (TLC), residual volume (RV) and vital capacity (VC) are the 3 parameters mainly determined for lung volumes by most pulmonary function studies.\(^5\) A proportional reduction in FEV\(_1\)/FVC with a reduction in TLC confirms the presence of a restrictive pathologic process. DLCO is a measure of a patient’s ability to absorb alveolar gases into the capillary blood flow, which is influenced by alveolar membrane thickness, hematocrit level, cardiac output, and the uneven distribution of ventilation and perfusion over different lung regions.\(^6\) A reduction in DLCO is the most common functional abnormality, and it can be associated with thoracic irradiation, chemotherapy toxicity, idiopathic pneumonia, and graft-versus-host disease (GVHD).

Although pulmonary function studies have been widely used in HSCT patients, it should be noted that there are limitations in using the abovementioned tests to make conclusions in any patient.\(^3,7\) A good quality control program is indispensable in the laboratory where these pulmonary function tests are performed. This is especially critical when serial tests are used for comparison in the same patient, i.e. inter- and intraindividual variation over time. Any reported result must be generated from a test with a stringent procedure of merit. Clinicians should be aware that the results of pulmonary function studies are generally reported as a percent of predicted normal values. Each laboratory should have its own reference data or predicted normal values calculated from a population similar to the patients to be studied rather than using reference data generated from a different laboratory or a different population. The DLCO should also be interpreted after correction for hemoglobin, which is particularly important for HSCT patients.

For clarifying the value of using pulmonary function tests to predict or monitor patients’ lung condition after HSCT, investigators must recruit a large cohort of patients for study and utilize both pre-transplant and...
adequate periodical post-transplant data from a laboratory with well-controlled quality.3,7 This, however, is very difficult to achieve for most investigators. As a result, 2 studies that had aimed to study the evolutionary change of pulmonary function after HSCT including DLCO were unable to come to any conclusions.8,9 However, a reduction in DLCO at 2 years was found to be associated with the presence of chronic GVHD.9

Many other studies have been conducted to determine if pre-transplant pulmonary function could become a risk factor for post-transplant pulmonary complications and, even more, in predicting post-transplant mortality. The results of most studies agree that pre-transplant pulmonary compromise is associated with an increase in post-transplant morbidity.1–4 These results have prompted transplantation oncologists to perform pulmonary function tests before and after transplantation.

In this issue of the Journal of the Chinese Medical Association, Chang et al report a retrospective analysis of prospectively collected results of pulmonary function tests including FEV1 and DLCO in context with clinical data in acute lymphoblastic leukemia patients who received bone marrow transplantation (BMT) between August 1983 and February 2005 in a single institute in Taiwan.10 The strengths of their study are: all patients had the same disease and received the same procedure of BMT; the protocols were homogeneous; and patients received pre- and post-transplant pulmonary function studies longitudinally. Assuming that the laboratory where the pulmonary function tests were performed has a good quality control program and complied with American Thoracic Society recommendations, and with all the results having been carefully interpreted by a pulmonologist,4–7 there remain several issues that need to be addressed. This was a relatively small study, including only 32 patients. Twenty-three patients were excluded from the original cohort of 55 patients for the final analysis due to early death after BMT or not-in-complete-remission status upon receiving BMT. Unfortunately, the authors did not report the causes of those early deaths, which could have been due to either infectious or non-infectious etiologies. Is it possible that the reduction in DLCO is just a long-term complication that is only observed in long-term survivors? Since a significant association between decreased DLCO and chronic GVHD has been reported, and GVHD may carry a graft-versus-leukemia effect, it is possible that DLCO reduction could be a consequence of alloreactive activities associated with a longer survival. The definition of overall survival (OS) in this study was the interval between diagnosis and death rather than the interval between BMT and death. Although in univariate analysis, the authors showed that months-to-BMT after diagnosis was not a risk factor for OS, it could still have produced bias in such a small cohort of patients. What the authors have not shown in this paper are data on pre-transplant DLCO, the severity of DLCO reduction in each patient, and the interval between DLCO reduction and BMT in each patient.

Over the last decade, peripheral blood stem cell transplantation (PBSCT) has been used more widely than BMT to treat leukemia patients. Non-myeloablative HSCT has also been accepted as an alternative to myeloablative HSCT. It is not known if the data presented by Chang et al could be applied to acute lymphoblastic leukemia patients who receive PBSCT or non-myeloablative SCT with a variety of different conditioning regimens. Although the information provided by Chang et al deserves appreciation, it certainly needs to be validated in a large cohort of patients and, probably, tested in an animal model.

References


