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Correlation and Agreement of Handheld Spirometry with Laboratory Spirometry in Allogeneic Hematopoietic Cell Transplant Recipients

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A B S T R A C T

Early detection of subclinical lung function decline may help identify allogeneic hematopoietic cell transplant (HCT) recipients who are at increased risk for late noninfectious pulmonary complications, including bronchiolitis obliterans syndrome. We evaluated the use of handheld spirometry in this population. Allogeneic HCT recipients enrolled in a single-center observational trial performed weekly spirometry with a handheld spirometer for 1 year after transplantation. Participants performed pulmonary function tests in an outpatient laboratory setting at 3 time points: before transplantation, at day 80 after transplantation, and at 1 year after transplantation. Correlation between the 2 methods was assessed by Pearson and Spearman correlations; agreement was assessed using Bland-Altman plots. A total of 437 subjects had evaluable pulmonary function tests. Correlation for forced expiratory volume in 1 second (FEV_1) was r = .954 ($P < .0001$) at day 80 and r = .931 ($P < .0001$) at 1 year when the handheld and laboratory tests were performed within 1 day of each other. Correlation for handheld forced expiratory volume in 6 seconds (FEV_6) with laboratory forced vital capacity was r = .914 ($P < .0001$) at day 80 and r = .826 ($P < .0001$) at 1 year. The bias, or the mean difference (handheld minus laboratory), for FEV_1 at day 80 and 1 year was −.13 L (limits of agreement, −.63 to .37) and −.10 L (limits of agreement, −.77 to .56), respectively. FEV_6 showed greater bias at day 80 (−.51 L [limits of agreement, −1.44 to .42]) and 1 year (−.40 L [limits of agreement, −1.81 to 1.01]). Handheld spirometry correlated well with laboratory spirometry after allogeneic HCT and may be useful for self-monitoring of patients for early identification of airflow obstruction.

INTRODUCTION

More patients are surviving after allogeneic hematopoietic cell transplantation (HCT) for the treatment of hematologic malignancies and associated disorders [1]; however, late onset noninfectious pulmonary complications, such as cryptogenic organizing pneumonia, interstitial pneumonitis, and bronchiolitis obliterans syndrome (BOS), a manifestation of chronic graft-versus-host disease (cGVHD) that affects up to 14% of those with extrapulmonary cGVHD, remain a significant cause of morbidity and mortality [2-6]. These complications often present at an advanced stage of disease when the underlying process is irreversible [7].

Early detection of pulmonary function changes after HCT may identify a subset of patients at highest risk for late pulmonary complications. For instance, lung function decline at day 80 after transplantation is associated with development of cGVHD within 1 year and a higher risk of nonrelapse mortality within 5 years [8]. Detection of at-risk populations may facilitate pre-emptive treatment or participation in clinical trials at a stage when the disease

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process may be reversible. However, frequent spirometric monitoring through a pulmonary function laboratory or an office setting can be expensive and inconvenient for the patient.

An alternative approach is self-monitoring with a handheld spirometer, which is portable, inexpensive, and easy to use, thereby permitting more frequent testing [9-11]. In recipients of lung transplantation, weekly self-monitoring with a handheld spirometer has been shown to detect BOS at an earlier stage than clinic spirometry, enabling initiation of treatment earlier in the disease course [12]. We evaluated whether this approach can be applied to an HCT population, including pediatric patients, by comparing handheld spirometry with laboratory spirometry in a cohort enrolled in a prospective study performed during the first year after allogeneic HCT.

METHODS

Study Design

Patients were enrolled in a prospective, observational, longitudinal study conducted at Fred Hutchinson Cancer Research Center and the Seattle Cancer Care Alliance (SCCA) designed to follow the natural history of community-acquired respiratory virus infection and airflow decline in allogeneic HCT recipients, as previously described [13]. The institutional review board of Fred Hutchinson Cancer Research Center approved the study protocol (1587.00). Allogeneic HCT candidates undergoing transplantation between December 2005 and February 2010 were eligible. Enrolled patients ≥6 years of age performed pulmonary function and laboratory studies just before HCT and subsequently on a regular basis for 12 months. As part of routine transplantation care, patients underwent extensive pretransplantation evaluation and were required to reside in Seattle during and after their transplantation procedure, until discharge around 80 days after transplantation. Clinical follow-up after discharge was arranged at the discretion of the primary providers. Patients were offered a long-term follow-up evaluation at the SCCA at 1 year after transplantation.

Clinical Data

Demographic and clinical data were prospectively collected in a research database. Conditioning regimens were categorized as myeloablative plus total body irradiation, myeloablative non–total body irradiation, or nonmyeloablative. Underlying disease risk was categorized as low, intermediate, and high risk according to previously published criterion [14]. Smoking status was categorized as current, former, never, or unknown at the time of transplantation. Acute GVHD severity was scored according to an established symptoms-based scoring system [15]. cGVHD was categorized as present or absent according to National Institutes of Health consensus guidelines [16].

Spirometry Protocol

At enrollment, participants were instructed on the use of a portable electronic handheld spirometer commonly used in monitoring patients with asthma (KoKo Peak Pro-6, Ferraris Respiratory, Louisville, Colorado, or PiKo-6, Pulmonary Data Services, Inc., Louisville, Colorado), chosen for affordability, ease of use, and small size. Patients were asked to perform handheld spirometry once before HCT and then on a weekly basis for 1 year after HCT. Before discharge at day 80, patients performed handheld spirometry in the presence of a study coordinator. Patients made 3 consecutive attempts for each test. Handheld spirometry results performed at home were recorded on a weekly symptom log and relayed to the study coordinator by mail, phone, or online survey. All standard pulmonary function tests (PFTs) were performed at the SCCA outpatient PFT laboratory (Sensormedics, Yorba Linda, California) per American Thoracic Society/European Respiratory Society guidelines [17] at 3 time points as part of standard clinical management at SCCA: baseline (before transplantation), day 80 after HCT, and 1 year after HCT.

Analysis of Spirometry

Laboratory tests performed closest to the date of transplantation at baseline, day 80 ± 40, and day 365 ± 120 were used for analysis. The handheld spirometry performed closest to the laboratory test and within these time windows was selected for comparison. Patients were excluded from the spirometry analysis if handheld forced expiratory volume in 1 second (FEV_1) or forced expiratory volume in 6 seconds (FEV_6) values were not available. Because the handheld spirometer only measured FEV_1 and FEV_6, FEV_6 was used as a surrogate for forced vital capacity (FVC) in the analysis. The best of 3 handheld FEV_1 and FEV_6 values for each time point was used. To reduce the impact of a time interval on the comparison of handheld with laboratory spirometry, subset analyses were performed on subjects with data that fell within the lower quartile of time interval between handheld and laboratory values at baseline, day 80, and 1 year ("subset 1"). To simulate a screening situation in which handheld spirometry precedes laboratory spirometry for the post-transplantation time period, analysis was performed on a second subset ("subset 2") where only post-transplantation handheld data greater than the lower quartile of time interval but less than 14 days before the laboratory spirometry at day 80 and 1 year were considered. Subsets of pediatric subjects (<20 years old) ages 6 to 13 and ages 14 to 19 were also analyzed. Percent predicted values were calculated using the third National Health and Nutrition Examination Survey (NHANES III) [18] formulas as recommended by American Thoracic Society guidelines [19].

Statistical Analysis

Pearson and Spearman correlation coefficients were calculated and linear regression plots were used to compare handheld with laboratory values. Agreement between the 2 techniques was illustrated using Bland-Altman plots, which display the difference between the handheld and laboratory values plotted against the mean value of the 2 test values. *Bias*, the degree to which the methods differ from 1 another, was defined as the mean difference between measures, and associated 95% confidence intervals (CI) of the bias (mean difference ± 1.96 multiplied by the standard error of the mean) were calculated. Bland-Altman plots are accompanied by upper and lower limits of agreement, which reflect the variation of bias within a sample and are defined by the 95% CI for the differences (mean difference ± 1.96 multiplied by the standard deviation of the difference) [20]. All statistical analyses were performed using SAS 9.3 for Windows (SAS Institute, Inc., Cary, NC).

RESULTS

Study Cohort

The total number of patients enrolled was 571 of whom 437 had PFTs available for analysis (Figure 1). Baseline characteristics are shown in Table 1. Pediatric subjects represented 10% (43 of 437) of the total cohort. Of the 437 subjects, 38 (9%) died by day 80 and 147 (34%) died by 1 year.

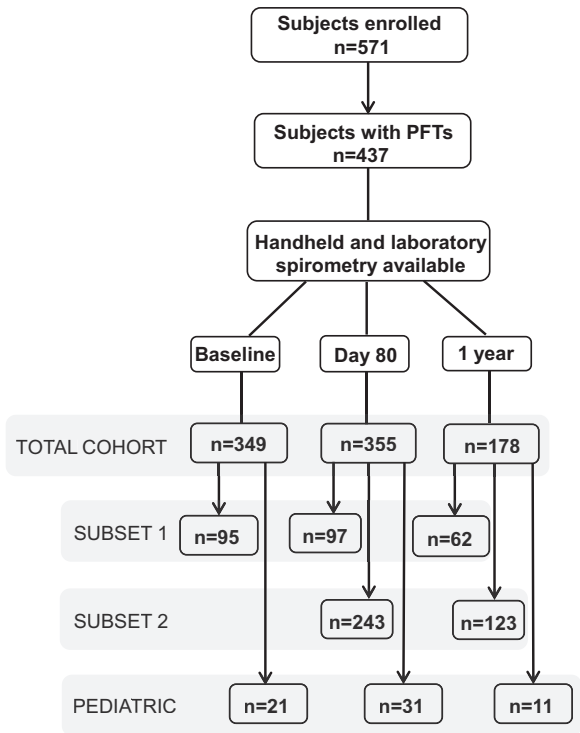

Figure 1. Study cohort and subsets at 3 time points in relation to allogeneic HCT.