

Results of quantitative chest-CT in chronic pulmonary graft-vs.-host disease (cGvHD) 3 years after allogeneic stem cell transplantation

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Background: To quantify lung parenchymal changes in symptomatic patients with chronic pulmonary graft-versus-host disease 3 years after allogeneic stem cell transplantation (allo-SCT) by means of CT-densitometry (CTD) and to compare results with those of established pulmonary function tests (PFT).

Methods: The study group consisted of 26 patients with pulmonary cGvHD (19 males, 7 females; mean age, 49.29±15.89; range, 19–72 years). The diagnosis was based on clinical symptoms, PFT and chest-CT findings. CTD and PFT were performed both in the pre- and post-transplantation setting and results compared with each other. CT scans were obtained during suspended deep inspiration including the whole lungs. The mean lung attenuation (MLD), low attenuation values (LAV) and distribution of focal parenchymal abnormalities compatible with emphysema (HU <−950) were quantitatively calculated with histograms and graphics. On PFT, total lung capacity (TLC), residual volume (RV), vital capacity (VC), forced expiratory volume in 1 s (FEV1s) and diffusion capacity for carbon monoxide (DLCOSB) were registered.

Results: Changes in end-inspiratory lung volume and density (MLD and LAV) in symptomatic cGvHD patients in mean three years after allo-SCT proved all not significant, but there was a clear trend towards an increase in lung volume and a decrease in lung attenuation. These results were similar throughout all classes of bronchiolitis obliterans (BO) by cGvHD. PFT showed a significant decrease in VC, FEV1s but only a minimal decrease in DLCOSB. Changes in FVC after stem cell transplantation correlated with changes in LAV (r=0.649, P=0.031). Predicted VC correlated with changes in LAV (r=0.771, P=0.005). There was a correlation between the absolute difference of FEV1 and DLCOSB (r=0.64, P=0.14) before and after stem cell transplantation.

Conclusions: End-inspiratory phase CT lung parenchyma quantification in symptomatic patients with pulmonary cGvHD 3 years after allo-SCT shows discrete changes over the pre-transplantation setting representing airway obstruction, mirroring airflow limitation on PFT. Its use enables exclusion of relevant parenchymal destruction (emphysema-equivalent lung density) at this time.

Keywords: HRCT; chronic graft-versus-host disease; allogeneic stem cell transplantation (allo-SCT); CT-densitometry (CTD)

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Introduction

Patients undergoing allogeneic stem cell transplantation (allo-SCT) are often confronted with various pulmonary complications that are usually subdivided into infectious and non-infectious as well as in early and late phase considering the time point of transplantation (1). In 40–60%, significant clinical affection with respiratory impairment can be observed (2,3). The major late post-transplantation complication is chronic pulmonary graft-vs.-host disease (cGvHD). It is one of the most frequent non-infectious late-onset complications which benefits from immunosuppressive therapy (4). Different subgroups have been described depending on clinical, radiological, histopathological findings, as well as pulmonary function tests (PFT). The most cited classification has been proposed by Palmas *et al.*, who subdivided cGvHD into bronchiolitis obliterans (BO), BO with organizing pneumonia (BOOP), diffuse alveolar damage (DAD), lymphocytic interstitial pneumonia and interstitial pneumonia (5). In different publications, BO is equalized to an end-stage form of cGvHD (5). Current guidelines define chronic in contrast to acute types of GvHD by the absence of an acute course of the disease (6). BO as the dominant manifestation of cGvHD is defined as a reduced forced expiratory volume in 1 s (FEV1) (<75% of the predicted value), reduced relation of FEV1/vital capacity (VC) (<5–7 percentile of predicted value), evidence of air-trapping or small airway thickening on chest-CT and the absence of opportunistic pulmonary infections (6). In patients with already known cGvHD, the evidence of air-trapping or small airway thickening is no longer necessary. Whereas documentation of air-trapping requires generally the use of expiratory chest-CT measurements, the presence of bronchial wall thickening and luminal dilatation may be discrete or absent in the early stages of BO. Finally, the diagnosis of obstructive disease is knowingly the domain of expiratory tests both for PFT and chest-CT. Nevertheless, end-inspiratory chest-CT studies are practiced frequently in this patient group after allo-SCT mainly for exclusion of pulmonary infection and they are more accurate for detection of emphysema-equivalent lung parenchymal changes representing advancing pulmonary tissue destruction. As quantification of lung volume and density (attenuation) is now available as a post-processing tool for most CT-scanners this additionally gained information might be helpful for diagnosis of cGvHD.

Hence, the purpose of this study was to evaluate the role of end-inspiratory chest-CT data quantification in the early diagnosis of BO by comparison with established PFT

changes occurring on average three years after allo-SCT.

Methods

Patient characteristics

Between September 2004 and July 2014, we retrospectively analysed 26 patients with chronic pulmonary GvHD (19 males, 7 females; mean age, 49.29±15.89; range, 19–72 years) at our institution that have been all examined by means of chest-CT and presented also with current PFT-data for methodical comparison. Indications for these examinations were respiratory complaints of unknown origin.

The local ethics board was informed and gave its written approval to this retrospective study, Local ethic aboard waived informed consent for his retrospective study (number of ethic votum 237/2015R). The underlying diseases of the cGvHD patients were: acute myeloid leukemia (n=12), acute lymphoblastic leukemia (n=4), myelodysplastic syndrome (n=2), chronic myeloid leukemia (n=2), multiple myeloma (n=2), non-Hodgkin lymphoma (n=1), chronic lymphocytic leukemia (n=1) and mantle cell lymphoma (n=1) and blastic plasmacytoid dendritic cell neoplasm (n=1). All underlying diseases are tabulated on *Table 1*.

All patients underwent a chest-CT in the pre-transplantation (before allo-SCT) setting. The mean age at time point of transplantation was 46.89±15.29. The time point of documentation of pulmonary cGvHD was 2.99±3.21 years after allo-SCT at a mean age of 49.29±15.89. The reason for the chosen control interval was that cGvHD is mostly an asymptomatic, insidious disease occurring within the first 2 years of SCT with clinical symptoms expected first in the subsequent time.

All our patients developed respiratory symptoms like chronic cough and exertional dyspnoea within the first three years after allo-SCT.

Stem cell transplant characteristics are tabulated on *Table 2*.

All patients received in the post-transplant setting different medications for GvHD- prophylaxis: 12 patients received mycophenolate-mofetil (MMF) (46.1%), 13 received tacrolimus (50.0%), 10 methotrexate (38.4%), 6 anti-thymocyte-globulin (ATG) (23.0%) and 7 cyclosporine (26.9%).

Clinically, a grade I cGvHD was diagnosed in 6 patients (23.0%), a grade II cGvHD was found in 2 patients (7.6%), a grade III cGvHD in 3 patients (11.5%) and a grade IV cGvHD in 2 patients (7.6%) documented either by manifestations of skin, liver, lung (42.3%) or gastrointestinal

Table 1 GvHD patient characteristics

Characteristics	N (%)
Median age (range), years	49.2±15.8
Sex, male/female	19/7
Underlying disease	
Acute myeloid leukemia	12 (46.1)
Acute lymphoblastic leukemia	4 (15.3)
Myelodysplastic syndrome	2 (7.8)
Chronic myeloid leukemia	2 (7.8)
Multiple myeloma	2 (7.8)
Non-Hodgkin lymphoma	1 (3.8)
Chronic lymphocytic leukemia	1 (3.8)
Mantle cell lymphoma	1 (3.8)
Blastic plasmacytoid dendritic cell neoplasm	1 (3.8)

GvHD, chronic pulmonary graft-vs.-host disease.

Table 2 Overview of stem cell transplant characteristics

Characteristics	n	%
Allogeneic	26	100
HLA identical sibling (10/10)	11	42.4
HLA matched unrelated (10/10)	11	42.4
HLA mismatched unrelated	2	7.6
HLA mismatch related	1	3.8
Haploidentical	1	3.8

tract.

The grade of BO in our patients was additionally scored in three stages based on the FEV1%pred: mild (60–79%), moderate (40–59%) and severe (39% or less) (6). In our cohort 13 patients (50.0%) had mild, 7 patients (26.9%) had moderate and 6 patients (23.1%) had severe form of BO based on this classification. Four patients received a biopsy of the lung because of rapidly deteriorating respiratory function and evaluation for potential lung transplantation. In the other patients, a biopsy was abandoned because of their clinical status.

High resolution CT-technique

For monitoring the disease course, repeated CT

examinations (56 CT-examinations containing 20 baseline-CT and 26 follow-up-CTs) were performed for the cGvHD patients.

CT-examinations were performed using helical CT-scanner scanner (Somatom Plus 4, Somatom 16, Somatom sensation 64, Somatom Definition AS+, Siemens Medical Systems, Erlangen, Germany) using a 250–330 mm field of view, a 512×512 reconstruction matrix, 120 kV, 100–150 effective mAs and a tube rotation time of 0.5/0.3 ms. No intravenous contrast-material was applied. A single spiral acquisition was obtained from the apex to the base of the lungs during one breath-hold at suspended end-inspiratory volume. Examinations were performed with patients in the supine position. Every CT scan was reconstructed at 3 mm slices with a sharp reconstruction algorithm (filter, B70) and 1 mm reconstruction increment for visual assessment and quantification (filter, B31f).

Imaging analysis

All scans were viewed at standard mediastinal windows (level, 35 HU; width, 450 HU) and lung windows (level, –700 HU; width, 1,500 HU). All examinations were viewed by one reader (MH) with 20-year experience in reading chest-CT. All patients received a quantitative imaging analysis of the lung parenchyma with the Syngo CT Pulmo 3D software (Siemens Healthcare). A CT densitometry is possible with this software (7–10). For each side, separated lung volumes and lung densities were measured. Both the percentages of lung volumes below –950 HU [low attenuation values (LAV)] and over –250 HU [high attenuation values (HAV)] were computed. Additional areas of emphysema were analysed based on their different volumes, which is called cluster analysis. Areas were classified into four subgroups based on their size (class 1 =2 mm³; class 2 =8 mm³; class 3 =65 mm³; class 4 =187 mm³). An example of cluster coded analysis (color coded display of emphysema equivalent attenuation values) is given on *Figure 1*.

Standard of reference

All patients underwent PFTs according to the European Respiratory society guidelines before and after intervention (11). A Masterscreen Body (CareFusion GmbH, Hoechberg, Germany) were used for the PFT before the stem cell transplantation, but also in follow up. Following PFT-parameters were assessed: VC, FEV₁, single-breath diffusion capacity for carbon monoxide

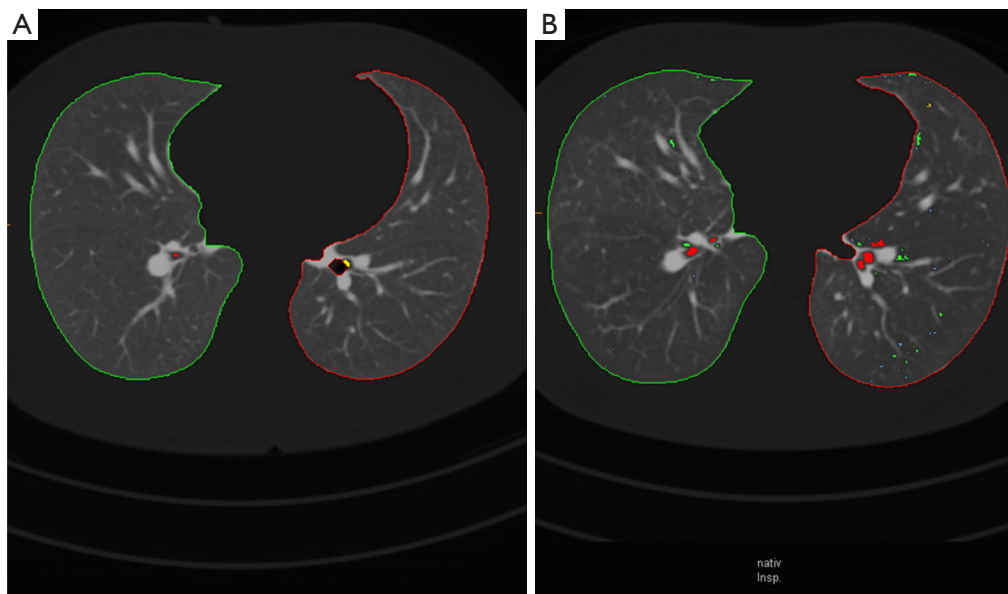


Figure 1 Axial CT images of a 32.5-year-old patient with chronic myeloid leukemia nine days after stem cell transplantation (A) and 23 months thereafter (B). Only few emphysema equivalent areas occurring after allo-SCT are found in the cluster analysis (color coded display of emphysema equivalent attenuation values). Correspondingly, minimal changes in lung parenchyma attenuation (MLD from -799 to -839 HU, LAV = 0.0 to LAV = 1.4 and HAV = 1.2 to HAV = 1.4 before and after stem cell transplantation, respectively) were registered. Pulmonary function testing showed values before vs. (after) stem cell transplantation: VC IN 4.79 mL (3.35 mL), FVC 4.81 mL (3.18 mL), FEV1 4.04 mL (1.8 mL) and FEV1%VC 84.51 (53.63). SCT, stem cell transplantation; MLD, mean lung attenuation; LAV, low attenuation value; VC, vital capacity; FVC, forced expiratory vital capacity; FEV1, forced expiratory volume in 1 s.

($DLCOC_{SB}$), single-breath diffusing capacity for carbon monoxide divided by the alveolar volume ($DLCOC_{SB}/VA$) and percentage of the measured values to the predicted values (Pre).

Statistics

All results are expressed as average with standard deviation. Statistical analysis was performed using dedicated software [IBM SPSS 16.0 (SPSS), Armonk, USA]. The Kolmogorov-Smirnov test was used for the normality test including Lilliefors significance correction. Wilcoxon signed rank test was used for significance testing concerning total lung volume. Paired t -test was used for significance testing MLD, LAV, HAV and cluster analysis before and after stem cell transplantation. Paired t -test was used for significance testing concerning PFT-parameters before and after stem cell transplantation. Pearson's r coefficients were determined for correlation analysis between total lung volumes with MLD, LAV and HAV. A value of $P < 0.05$ was considered significant.

Results

Patient's data

The clinical parameters of cGvHD-patients before and after stem cell are shown on *Table 3*.

Lung volumes and densities in cGvHD

Lung volumes at end-inspiration in cGvHD patients were $5,862.64 \pm 1,472.70$ mL before stem cell transplantation and $5,934.0 \pm 1,169.18$ mL after transplantation ($P = 0.317$).

Mean end-inspiratory MLD values in cGvHD in the pre-transplantation setting were -842.29 ± 24.29 HU. MLD values decreased after allogeneic-SCT from -823.30 ± 38.01 to -842.29 ± 24.29 HU; however, this did not reach statistical significance ($P = 0.26$).

Accordingly, LAV values in cGvHD patients were 2.58 ± 4.38 before stem cell transplantation. After stem cell transplantation, no significant differences in LAV were measured (3.53 ± 8.77 vs. 2.58 ± 4.38 ; $P = 0.182$).

HAV values in cGvHD patients were 1.24 ± 0.66 . No significant differences in HAV were measured (1.2 ± 0.49 vs.

Table 3 Listed clinical parameters including PFT in patients with GvHD of the lung (n=26)

Parameters	Before transplantation		After transplantation		P
	Mean	SD	Mean	SD	
VC, mL	4.26	1.15	3.18	0.95	<0.001*
VC % predicted	89.26	16.05	71.26	19.27	<0.001*
FVC, mL	4.11	1.22	3.02	0.95	<0.001*
FVC % predicted	90.70	20.45	70.22	19.54	<0.001*
FEV1, mL	3.32	1.27	2.10	0.98	<0.001*
FEV1% predicted	88.28	28.16	59.75	25.14	<0.001*
FEV1%VC	77.06	15.27	65.05	18.24	0.031*
FEV1%VC predicted	96.60	19.21	82.62	23.00	<0.001*
DLCOC _{SB}	7.98	2.00	6.30	1.91	0.009*
DLCOC _{SB} % predicted	75.13	16.32	63.36	21.78	0.009*
DLCOC _{SB} /VA	1.29	0.42	1.23	0.33	0.043*
DLCOC _{SB} /VA% predicted	83.01	25.88	81.63	20.16	0.112

*, means statistically significant (P<0.05). VC, vital capacity; FVC, forced expiratory vital capacity; FEV1, forced expiratory volume in 1 s; DLCOC_{SB}, single-breath diffusion capacity for carbon monoxide; DLCOC_{SB}/VA, diffusing capacity for carbon monoxide divided by the alveolar volume; Pre, percentage of the measured values to the predicted values.

1.125±0.56 HU) after stem cell transplantation, however a tendency to a decrease was registered (P=0.238).

Cluster analysis

The cluster analysis (color coded display of emphysema equivalent attenuation values depending on their size) revealed no significant differences in the values of cGvHD patients before and after stem cell transplantation. Only the cumulative values (class 1–class 4) for the lung parts showed a tendency of an increase of the values (P=0.105 left lung; P=0.108 right lung which represents the overall LAV values.

Between the different BO grade I–III subgroups, there was a significant difference between the HAV (P=0.03) which declines with higher group-score; however no differences between lung volumes, LAV or mean lung density were observed.

Correlation of CTD with PFT

Absolute differences in forced expiratory vital capacity (FVC) before and after stem cell transplantation showed positive correlations with changes of LAV (r=0.649, P=0.031). Predicted VC correlated accordingly positive with changes of LAV (r=0.771, P=0.005). There was no statistically significant correlation between LAV and DLCOC_{SB}, however a tendency towards a growing negative

correlation after transplantation (after transplantation, r=-0.354, P=0.115).

There was a correlation between the absolute difference of FEV1 and DLCOC_{SB} measured in each patient (r=0.64, P=0.14) before and after stem cell transplantation.

Between the different degrees of BO (grade I–III), gender and underlying disease there were no statistical significant differences or correlations.

Discussion

The pathophysiological mechanism in chronic pulmonary GvHD is obstruction caused by progressive fibroproliferation within the terminal bronchioles in the lung leading to stenosis and obliteration of airway lumens (12). Accordingly, the diagnostic criteria for lung GvHD include both clinical, imaging as well as pulmonary functional test parameter that consider in the first line changes related to secondary bronchial obstruction (13). Airflow obstruction may lead if untreated rapidly to irreversible lung damage with a 5-year survival rate as low as 13% (14). Increased resistance to expiratory airflow causes with time parenchymal destruction with decrease of oxygen exchange area in the lung and restriction. Therefore, anticipation of cGvHD-related pulmonary

changes is mandatory for preventing rapid decline in lung function and for institution of adequate therapy. Previous studies dealing with this post-transplantation complication used mainly CT-morphological criteria like the presence and extent of air-trapping and accompanying expiratory mosaic pattern, bronchial wall thickening (15,16) whereas a few also used novel lung density quantification software (17). Taking in consideration that many of these patients will develop at time different pulmonary complications mainly due to ongoing GvHD prophylaxis with immunosuppressive drugs, additional quantification of lung parenchymal volume and density on usual end-inspiratory chest-CTs could help to early detect cGvHD-related changes. Based on this assumption, we set out to retrospectively quantify lung parenchymal changes in patients fulfilling cGvHD (obstructive bronchiolitis) criteria that became symptomatic, in mean three years after allo-SCT (6). Our patients presented all with pulmonary obstructive disease occurring *de novo* in this given clinical setting confirmed by significant reduction of FEV1s, increase in RV accompanied by a not significant decrease in DLCO_{CSB}. Interestingly, the total lung capacity (TLC) did not change significantly at time. According to our results, lung volumes at end-inspiration in cGvHD patients slightly increased after transplantation to 5,862.64±1,472.70 *vs.* 5,934.0±1,169.18 mL (P=0.317). Correspondingly, the average end-inspiratory density (MLD) values decreased after allogeneic-SCT from -823.30±38.01 to -842.29±24.29 HU; however, they did not reach statistical significance. LAV values increased after stem cell transplantation from 2.58±4.38 to 3.53±8.77, but even these changes did not reach statistical significance. Notably, MLD, LAV and lung volume differences between pre- and post-transplantation phases proved also independent on the degree of BO (grade I-III). This is in support of obstructive *vs.* destructive parenchymal changes as the latter are expected to more markedly impact lung density (MLD and LAV). Statistically, the absolute differences in FVC before and after stem cell transplantation showed positive correlations with changes in LAV (r=0.649) whereas the predicted VC correlated positive also with LAV (r=0.771).

Little is known about the course of cGvHD in the first years after allo-SCT. Longitudinal studies have stated that there is first a decline in airflow, lung volumes and diffusing capacity up to 6 months after transplantation followed by partial recovery by 1–2 years and normal airflow between 2–13 years (18–20). Others have reported either no obstruction, but a low incidence of restriction (21) or no

obstruction coupled by a higher incidence of restriction (22). In our cohort, lung volume increased after allo-SCT at end-inspiration accompanied expectedly by a decrease in MLD and an increase in LAV. However, the magnitude of these changes proved not significant in our cohort, three years after allo-SCT. Notably, changes in diffusing capacity proved modest suggesting that obstruction is the leading mechanism in respiratory decline in cGvHD at this time point. This finding matches with the modest degree of emphysema equivalent (<-950 HU) areas (clusters) measured at CT-densitometry (CTD).

This study has some limitations. First, it is retrospective in character. Second, not all patients receiving repeated chest-CT in the post-transplantation clinical setting underwent also PFT, so we could not include all patients experiencing this pathology in the current evaluation. Third, we did not perform additional expiratory series in order to document obstruction by means of CT-lung parenchyma quantification.

CT-quantification at end-inspiratory phase obtained in cGvHD patients three years after allo-SCT shows only slight pathological changes (increase in lung volume and decrease in lung parenchymal attenuation) compatible with airflow obstruction. However, this technique enables exclusion of relevant parenchymal destruction (emphysema-like lung density) at this time.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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