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High Diagnostic Yield of Dedicated Pulmonary Screening before Hematopoietic Cell Transplantation in Children

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A B S T R A C T

Pulmonary complications are an important cause for treatment-related morbidity and mortality in hematopoietic cell transplantation (HCT) in children. The aim of this study was to investigate the yield of our pre-HCT pulmonary screening program. We also describe our management guidelines based on these findings and correlate them with symptomatic lung injury after HCT. Since 2008, all patients undergo a dedicated pulmonary screening consisting of pulmonary function test (PFT), chest high-resolution computed tomography (HRCT), and bronchial alveolar lavage (BAL) before HCT. We systematically evaluated the yield during the first 5 years of our screening program. We included 142 consecutive children. In 74% of patients, abnormalities were found. In 66% of patients, 1 or more PFT results were <80% of normal. Chest HRCT showed abnormalities in 55%; 19% of these abnormalities were considered "clinically significant." BAL was abnormal in 43% of patients; respiratory viruses (PCR) were found in 35 patients, fungi (antigen or culture) in 21, and bacteria (culture) in 22. All 3 screening tests contributed separately to clinically relevant information regarding pulmonary status in these pre-HCT children. In 46 patients (33%), screening results had diagnostic and/or therapeutic implications. We found an association between pre-SCT HRCT findings and lung injury after transplantation. Pre-HCT screening with the combination of 3 modalities, reflecting different domains of respiratory status (function, structure, and microbial colonization), reveals important abnormalities in a substantial number of patients. Whether this improves patient outcome requires further investigation.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is a curative treatment for various diseases. Pulmonary complications, both infectious and noninfectious, are frequently seen in patients undergoing HCT. In children, the incidence of pulmonary complications varies from 25% to 74% and is associated with a significantly increased risk for mortality [1-3]. Because of the risk of life-threatening complications of the procedure, patients are routinely screened for HCT eligibility. Lung screening can potentially impact selection of HCT patients as well as affect preemptive treatment and prognosis.

Invasive fungal infections (IFI) are an important cause of morbidity and mortality during HCT. Diagnostic imaging, culturing pathogens, and antigen detection can be helpful to identify patients at high risk for IFI, which may guide therapy [4].

Also, respiratory viruses (RV) may have impact on the overall survival of HCT, either directly as a cause of pneumonitis in the severe immune-compromised patient or indirectly by triggering allo-immunity in the setting of allogeneic transplantation [5].

In 2008, we implemented extensive pre-HCT lung screening, which includes pulmonary function test (PFT), chest high-resolution computed tomography (HRCT), and bronchial alveolar lavage (BAL) in all patients. Here, we evaluate the yield of such an extensive pulmonary screening

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program and describe our treatment guidelines according to these findings as well as the outcome of patients.

MATERIALS AND METHODS

All consecutive pediatric patients undergoing a first allogeneic HCT in our center between January 2008 and August 2013 were included. Patients were enrolled in the HCT research protocol after providing written informed consent for data collection and analysis, according to national ethical regulations (Ethical Commission Number 05/143 and 11/063K). Patient characteristics (age, gender, underlying disease), clinical symptoms, results of pulmonary screening tests, and occurrence of symptomatic lung disease after HCT was registered.

Pulmonary Screening

Standard pre-HCT pulmonary screening is performed in the week before transplantation and consists of a PFT, HRCT scan, and BAL.

PFT includes spirometry, whole body plethysmography, and measurement of carbon monoxide diffusion capacity. Measurements are performed in children aged 5 years and older, according to American Thoracic Society/European Respiratory Society criteria, using calibrated pneumotachometer systems (Jaeger, Hochberg, Germany). Values are expressed as percentage of predicted values for age, race, sex, and height-matched controls (The Utrecht data set, Koopman [6]).

Forced expiratory volume in 1 second, forced vital capacity, total lung capacity, and lung diffusion capacity for CO, corrected for hemoglobin and alveolar volume $<$ 80% of predicted values are considered to be abnormal. Residual volume of $>$25% of total lung capacity is considered to be abnormal and suggestive for trapped air. HRCT scans are acquired using a 16-detector row scanner (Philips Medical Systems, Best, Netherlands). For infants and young children, scans are obtained at 25-cm H^2O pressure (inspiration) and 0-cm H^2O pressure (expiration). For older children, who were able to cooperate with breath hold instruction, scans were obtained at full inspiration and at end of exhalation. Inspiration images are obtained using fixed 90 kVp and 18 to 60 mAs (depending on bodyweight). For expiration images, we used 90 kVp and 11 mAs. Acquisition was volumetric thin-slice for both inspiratory and expiratory computed tomography.

All HRCT scans were assessed by a pediatric radiologist. Fleischner Society terms for thoracic imaging were used [7]. All abnormalities, as stated in the radiology report, were registered. Those abnormalities with clinical implications, such as antimicrobial treatment, guided lung biopsy or diuretics, were defined as *clinically significant*.

BAL was performed under general anesthesia.

BAL fluid was cultured and processed in accordance with standard microbiological procedures. Galactomannan (GM) tests are performed using BioRad Platelia Aspergillus EIA. Any positive culture or GM levels $>$ .5 was considered to be abnormal.

Nucleic acids are extracted using the total nucleic acid protocol with the MagNA pure LC nucleic acid isolation system (Roche Diagnostics, Basel, Switzerland). For detection of RNA-viruses cDNA is synthesized by using MultiScribe reverse transcriptase and random hexamers (Applied Biosystems, Foster City, CA). Detection of viral and atypical pathogens was performed in parallel, using real-time PCR assays specific for the following viruses: bocavirus, Human herpesvirus–6, respiratory syncytial virus, influenzavirus A and B, parainfluenzavirus 1 to 4, rhinoviruses, adenoviruses, human coronavirus OC43, NL63 and 229E, human metapneumovirus, and Mycoplasma pneumoniae. Real-time PCR procedures were performed as described previously [8]. Any positive PCR is considered to be abnormal.

The total costs for the pulmonary screening were approximately 900 euro. Chest HRCT costs 300 euro, RV panel PCR 495, bacterial cultures 11 euro, GM 12 euro, PFT (complete) cost 48 euro.

For further analysis, patients were classified according to their risk for pre-HCT pulmonary problems, based on underlying disease, immune competence, infection risk, and pretreatment with potentially lung-toxic therapy. We distinguished 3 groups of patients: those with an inherited immune deficiency, those with a malignant disease and chemotherapy before transplantation, and those with inborn errors of metabolism, mild bone marrow failure, and malignancies without chemotherapeutic treatment.

Standard Antimicrobial Prophylaxis

Antibiotic prophylaxis involved daily ciprofloxacin and fluconazole, from the start of conditioning until the resolution of neutropenia. Additional prophylaxis against *Streptococcus viridans* was given with cefazoline in the mucositis phase. Empiric antibiotic treatment for febrile neutropenia included vancomycin and ceftazidime. *Pneumocystis jeroveci* pneumonia prophylaxis was started from 1 month after transplantation as cotrimoxazole 3 times a week. In case of positive serology for herpes simplex virus in all patients, and in case of positive serology for varicella zoster virus in cord blood transplantation recipients, prophylaxis with aciclovir was given. No other antiviral prophylaxis was given. In patients at high risk for IFI, according to our protocol, based on pretreatment, duration of neutropenia, and history of fungal infection, Aspergillus prophylaxis was given with daily voriconazole or twice weekly amphotericin B.

Practical Guidelines according to Findings on Pulmonary Screening

Patients with severely impaired PFT ($<$50% of normal) were considered to have an unacceptable high risk for treatment-related mortality and were excluded for HCT.

Patients with RV from BAL were considered to have a high risk for alloimmune-mediated lung syndromes. In elective HCT procedures, HCT was postponed until the RV was cleared. In other cases—when the underlying disease did not allow treatment delay—tapering of immune suppression after HCT was adjusted to prevent alloimmune-mediated lung syndromes. In cases with probable fungal disease (positive cultures or GM from BAL), antifungal treatment was considered. Patients with positive bacterial cultures from BAL were not treated, unless pulmonary symptoms developed. Bacterial culture results guide the choice of empirical antibiotic treatment for neutropenic fever after HCT.

In patients with nodular lesions on HRCT, lung biopsy was considered to identify the possible infectious cause and antimicrobial resistance pattern.

In patients with possible or proven IFI based on BAL findings, biopsy results, or HRCT findings, antifungal treatment was started and granulocyte transfusions or haploidentical stem cell support (combined with cord blood grafts) were considered.

Statistical Analysis

Calculation of mean values and standard deviation was done for PFTs. Comparing the results with predicted values for age, race, sex, and height-matched controls was done using *t*-test (test value 100%). Comparison of the means between the different disease groups was done using ANOVA. The chi-square test was used for comparison of proportions between 2 or more groups. Differences with a P value of $<$ .05 were considered statistically significant. Associations between pre-HCT pulmonary screening findings and clinically manifested lung injury after HCT were analyzed using Cox proportional hazard models. Dichotomous outcomes were used as dependent variables. Univariate predictors with a P value of $<$ .05 were used for multivariate analysis. All statistics were done using SPSS 21.

RESULTS

Patient Cohort

We included 142 consecutive children receiving a first allogeneic HCT. Apart from mild upper respiratory tract symptoms in some, all patients were asymptomatic for lung disease at the time of pre-HCT screening. Patient characteristics are shown in Table 1.

Table 1
Patient Characteristics

Characteristic	Value
Age, yr	
Median (range)	7.0 (.2-19.4)
Gender	
Female	54
Male	88
Underlying disease	
Immunedeficiency*	27
Leukemia/lymphoma	60
Bone marrow failure†, bone marrow disease without chemotherapy‡	30
Inborn error of metabolism§	25

* Immune deficiencies include combined immune deficiency, severe combined immune deficiency, hemophagocytic lympho histiocytosis, autoimmune lymphoproliferative syndrome, and chronic granulomatous disease. Leukemia includes acute lymphoblastic leukemia and acute myeloid leukemia.

† Bone marrow failure includes Fanconi anemia, congenital agranulocytosis, and thallasemia.

‡ Bone marrow diseases not pretreated with chemotherapy include myelodysplastic syndrome and juvenile myelomonocytotic leukemia.

§ Inborn errors of metabolism includes predominantly Hurler syndrome.