Statistical Analysis Plan

Trial Short Title	MinimALL
Trial Full Title	i**M**ag**IN**g of chemotherapy-**I**nduced **M**orphological and functional lung changes in childhood **A**cute **L**ymphoblastic **L**eukemia and Hodgkin`s disease
Funding	Internal
Trial Principle Investigator	Dr. med. A. Karow PD Dr. med. F. Knieling
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Table of content

1. Version History

Version

Version 1.1

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Protokollversionen

Date	Version	Authors	Changes
10.08.2023	1.0	Dr. med. A. Karow PD Dr. med. F. Knieling Dr. med. A. Dierl	
11.12.2024	1.1	Dr. med. A. Karow PD Dr. med. F. Knieling Dr. med. A. Dierl	Addition of the NCT-Number

2. Project summary

With increasing cure rates of childhood cancer there is growing recognition of late effects of treatments. However, there is a lack of non-invasive and child-friendly procedures that can indicate possible late damage. This study uses morphologic and free-breathing phase-resolved functional low-field (PREFUL) magnetic resonance imaging (MRI) to identify persistent pulmonary toxicity after treatment for childhood acute lymphoblastic leukemia (ALL), Hodgkin`s disease (HD) and allogeneic stem cell transplantation.

3. Scientific background

Currently, overall cure rates of therapy for childhood acute lymphoblastic leukemia (ALL) and Hodgkin`s disease (HD) exceed 80% [1]. Apart from the development of supportive measures and novel targeted therapies, this success is still based largely on the optimized and risk-adapted dosing and scheduling of conventional chemotherapeutic agents and addition of radiotherapy in patients with HD in case of suboptimal response. Even though, contemporary systemic and local treatment regimens are less intensive than previous therapies, they are still associated with diverse general and specific, acute and chronic organ toxicities such as cardiac dysfunction, osteonecrosis, neurocognitive impairment, and second malignant neoplasms [2]. With increasing cure rates has come growing recognition of such adverse late effects of treatment and a number of guidelines for long-term follow-up (LTFU) after childhood cancer therapy have been proposed [3]. During treatment and aftercare, however, only crude orienting investigations assessing organ function are foreseen by these recommendations and apart from physical examinations and laboratory analyses, echocardiography remains the only functional imaging measure routinely applied according to the current protocols for pediatric ALL and HD. It appears conceivable, that by such investigations, minor organ alterations could be missed and additional approaches comprising more sensitive structural or functional imaging would be essential to facilitate early recognition and possible timely management of developing still subclinical alterations.

We here hypothesize that morphologic and free-breathing phase-resolved functional low-field (PREFUL) MRI may identify persistent pulmonary toxicity after treatment for childhood ALL and HD, respectively. Therefore, we propose to perform a cross-sectional, prospective, single-center clinical pilot study using low-field MRI in children and adolescents during the first five years after the end of therapy. The results of this trial could contribute to the implementation of further investigation techniques in future standardized and structured LTFU care.

References

1. Erdmann F, Frederiksen LE, Bonaventure A, Mader L, Hasle H, Robison LL, et al. Childhood cancer: Survival, treatment modalities, late effects and improvements over time. Cancer Epidemiol. 2021;71(Pt B):101733. Epub 2020/05/29. doi: 10.1016/j.canep.2020.101733. PubMed PMID: 32461035.
2. Silverman LB. Balancing cure and long-term risks in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2014;2014(1):190-7. Epub 2015/02/20. doi: 10.1182/asheducation-2014.1.190. PubMed PMID: 25696854.
3. Gebauer J, Baust K, Bardi E, Grabow D, Stein A, van der Pal HJ, et al. Guidelines for Long-Term Follow-Up after Childhood Cancer: Practical Implications for the Daily Work. Oncol Res Treat. 2020;43(3):61-9. Epub 2020/01/14. doi: 10.1159/000504200. PubMed PMID: 31931503.

4. Study aims

Determination of the frequency of morphologic and functional lung parenchymal changes using low-field magnetic resonance imaging

Hypotheses:
- Lung parenchymal changes can be detected in pediatric and adolescent patients after completion of chemotherapy or chemotherapy and additional radiotherapy
- Patients with changes do not present with clinical symptoms

Primary Objective:
- To determine the frequency of morphologic lung parenchymal changes using LF-MRI.

Secondary Objectives:
- To determine the frequency of functional lung parenchymal changes using LF-MRI.
- Determination of the anamnestic frequency of clinical respiratory symptoms

Study type
Prospective, monocentric, diagnostic study

5. Target variables

Primary target variables:

LF-MRT	Changes of lung parenchyma

Secondary target variables:

LF-MRT	Functional lung parameters (Ventilation match/mismatch, Perfusion match/mismatch, combined defects)
Cardiopulmonary testing	Oxygen uptake (VO_2) peak oxygen uptake (VO_2max) Respiratory exchange ratio (RER) Ventilatory anaerobic threshold (VT2) Carbon dioxide output (VCO_2) Heart rate (HR) Heart Rate Reserve (HRR) Breath rate at VAT Breath rate reserve (BRR) minute ventilation (VE) O_2 Pulse Heart rate variability (HRV) Exercise capacity (Borg Scale) Capillary blood gases and lactate At time 0 and after 6 months
Blood sample	Blood count*, Enterocytes*, Liver enzymes*, Retentionparamters*
Pulmonary tests	Lung function (VC%, FEV1%)
Clinical parameters	Age* Gender* Weight* Ethnicity* Time from therapy initiation/Interval until LF-MRI Current medication* Secondary diagnoses* Clinical examination*

*Standard procedures/parameters routinely available in follow-up care

6. Study design

Monocentric / multicentric

This is a monocentric study

Study arms: intervention/control

Patients (early and late effects) fulfilling the inclusion criteria will receive an MRI of the lungs and lung function testing

Randomization

Randomization is not planned

Blinding

Blinding to the study is not possible. Blinding of patients/subjects is not necessary

7. Study population

In- and exclusion criteria

Early therapeutic effects	Late therapeutic effects	Effects of hematopoietic stem cell transplantation
Planned number of patients		
N=10 ALL N=10 HD	N=10 ALL N=10 HD	N=10
Inclusion criteria		
- Diagnosed acute lymphatic leukemia or Hodgkin`s disease (HD) - Completed induction therapy or radiotherapy - From 5 years to <18 years	- Diagnosed acute lymphatic leukemia or Hodgkin`s disease (HD) - Completed intensive therapy or radiotherapy - From 5 years to <18 years	- Diagnosed acute lymphatic leukemia - Completed hematopoietic ste cell transplantation - From 5 years to <18 years
Exclusion criteria		
- Pregnancy, Lactation - Known pleural or pericardial effusion - Critical condition (requiring respiratory support, ventilation, oxygen, shock, symptomatic heart failure) - Marked thoracic deformities/malformations - Previous lung surgery - Injuries that do not allow physical stress diagnostics	- Pregnancy, Lactation - Known pleural or pericardial effusion - Critical condition (requiring respiratory support, ventilation, oxygen, shock, symptomatic heart failure) - Marked thoracic deformities/malformations - Previous lung surgery - Injuries that do not allow physical stress diagnostics	- Pregnancy, Lactation - Known pleural or pericardial effusion - Critical condition (requiring respiratory support, ventilation, oxygen, shock, symptomatic heart failure) - Marked thoracic deformities/malformations - Previous lung surgery - Injuries that do not allow physical stress diagnostics

- Rejection of MRI imaging - General contraindications for MRI examinations (e.g. electrical implants such as cardiac pacemakers or perfusion pumps, etc.)	- Rejection of MRI imaging - General contraindications for MRI examinations (e.g. electrical implants such as cardiac pacemakers or perfusion pumps, etc.)	- Rejection of MRI imaging - General contraindications for MRI examinations (e.g. electrical implants such as cardiac pacemakers or perfusion pumps, etc.)

Recruitment channels and measures

Patients (and parents) will be informed about the possibility to participate in the study in public notices and announcements on the homepage of the hospital as well as when visiting the pediatric clinic for hematology and oncology (including its outpatient clinics). If patients and their parents are interested to participate, they will be fully informed about the aims and methods (especially about the scientific/explorative nature of the study), the benefits and risks, and the revocability of participation in the study before giving their consent prior to study initiation. Patients in childhood and adolescence are additionally informed and educated about the study and its procedure in an age-appropriate manner.

8. Biometry

Explorative, hypothesis-generating study

Power calculation

No power calculation was performed as part of a pilot study. So far, there are no reliable preliminary data/measurements or similar to have conclusions about the frequency of possible changes. Therefore, in the context of this pilot study, a N=10 per group (patients with ALL, patients with HD, and patients after allogeneic hematopoietic stem cell transplantation) is considered reasonable.

Statistical Methodology

Continuous variables will be reported as mean with standard deviation, categorical variables as numbers with percentages if necessary. The occurrence of MRI changes is reported as a percentage of the population. All analyses are performed using GraphPad Prism (version 7.00 or later, GraphPad Software, La Jolla, CA, USA), RStudio (version 1.1.456 or later, RStudio Inc., Boston, MA, USA), or IBM SPSS Statistics (version 24 or later, IBM Corp., Armonk, NY, USA).

9. Statistical Analysis

Primary Objective:

The occurrence of morphologic lung parenchymal changes is given as a percentage of the study sample.

Secondary Objectives:

To determine the anamnestic frequency of clinical respiratory symptoms, results are reported as a percentage of the study sample.

To test for differences in early versus late therapy-induced changes in functional MRI parameters (V/Q Mismatch) and results of Cardiopulmonary/pulmonary/myocardial testing, a nonparametric Mann-Whitney U test is used for pairwise comparisons. For the comparison of therapy-induced changes between different oncological diseases, a nonparametric Kruskal-Wallis test is performed. $P < .05$ is considered to indicate statistically significant difference in all analyses.