Identification of paediatric Hodgkin lymphoma biomarkers and novel therapeutic targets.

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lymphomas Hodgkin's disease
Study type	Observational non invasive

Summary

ID

NL-OMON54726

Source
ToetsingOnline

Brief title
Hodgkin-biomarkers

Condition

- Lymphomas Hodgkin's disease

Synonym
Hodgkin disease, Hodgkin lymphoma, malignant lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Stichting Ferenc

Intervention

Keyword: Biomarkers, Hodgkin Lymphoma, Hodgkin Reed Sternberg cell, Micro-environment

Outcome measures

Primary outcome

1. Genetic analysis of HRS cells

By whole exome sequencing genetic alterations in malignant HRS cells will be discoverd. The changes of genomic material will be investigated and associated with existing oncogenes. The role of the genetic alterations for example in antigen presentation, chromosome integrity, transcriptional regulation and ubiquitination will be specified. If there are genes frequently mutated in the HRS cells, the role of these genes will be further explored. Genomic alterations will be correlated with therapy to response.

2. Tissue microenvironment

Tissue samples will be examined to confirm expression of PD-1/PD-L1 and TARC by Hodgkin tumor cells. T-cell subpopulations, NK-cells, macrophages and immune inhibitory cytokines such as IL1-10 and TGF will be examined on tissue samples. These laboratory finding will be correlated with clinical course and outcome.

3. Blood biomarkers

Levels of several serum proteins and cfDNA will be evaluated in HL patients and will be compared to controls to identify new biomarkers. These biomarkers will be correlated to staging, histology, presence of B symptoms, laboratory parameters and metabolic volume on FDG-PET. The value of TARC will be

investigated as diagnostic marker for pediatric HL. Therefore, we will determine normal values of TARC pediatric patients without HL. We will investigate the sensitivity and specificity of TARC as a diagnostic biomarker in patients with pediatric HL.

Second, the value of TARC as a disease response markers will be investigated by comparing it with FDG_PET scans during treatment. Finally TARC will be analyzed after treatment and during follow-up to investigate its value as markers for disease recurrence. If feasible, joint modelling for longitudinal TARC data and time-to-recurrence data will be done in order to investigate how changes in TARC influence the occurrence of a recurrence. In addition, predicted individual-specific biomarker values and recurrence-free survival probabilities can be obtained

Secondary outcome

Not applicable.

Study description

Background summary

Although classical Hodgkin Lymphoma (CHL) in paediatric patients has a good prognosis, the outcome is associated with a substantial proportion of treatment-related toxicity and still about 10-20% of the patients progress during or relapse after treatment. Strikingly, therapeutic regimens have not changed much during the past decades. Current treatment protocols rely on chemo- and radiotherapy, whereby patients are classified at diagnosis into three different treatment groups based on a clinical staging system. Radiotherapy can be omitted based on Fluoro-Deoxyglucose-Positron emission tomography CT (PET-CT) treatment response.
HL is considered an immunological disease, where reactive cells in the tumor microenvironment greatly outnumber malignant Hodgkin- and Reed-Sternberg (HRS) cells. The microenvironment supports proliferation and survival of HRS cells.

Due to active crosstalk between HRS cells and their microenvironment, serum biomarkers should be detectable and may be a surrogate for lymphoma viability. HL biology impedes development of in vitro and in vivo assays for functional studies to discover new therapeutics. Genetic analysis of malignant Hodgkin cells has been hampered by their scarcity and has largely been done with laser-dissected samples. In addition, apart from a clinical staging system at diagnosis, there have been no prognostic molecular markers to stratify patients into different therapy groups. Taken together this calls for efforts to identify biomarkers and get an in-depth understanding of HL immunology and biology to discover new therapeutic targets en less toxic therapies.

Study objective

The aim of this project is to identify biomarkers and novel therapeutic targets for pediatric Hodgkin lymphoma. To achieve this aim we defined three objectives:

1.Hodgkin Reed-Sternberg cells: To perform whole exome sequencing and gene expression arrays of FACS-sorted malignant Hodgkin and Reed-Sternberg cells. To get insights in the genetic profile of HRS cells and possibly translate this into feature therapeutic targets.

2. Tissue microenvironment: To investigate the tumor microenvironment by immunohistochemistry and gene expression profiling of microenvironment-derived T-cells. Hereby identification and validation of new markers (TARC, PD-1). This will possibly translate into novel therapeutic targets, for example PD-1-blocking antibody.

3. Serum biomarkers: To investigate the value of serum TARC, other biomarkers and ctDNA (see table 1 of the protocol) as disease response markers after each cycle of chemotherapy and directly compare it to PET-scans, which is used for response assessment in the current protocol. Analysing of serum samples after treatment and during follow-up to investigate its value as markers for disease recurrence.

Study design

In this multi-centre study, patients will be recruited from 5 paediatric oncology centers in the Netherlands. Based on the incidence of HL, we expect to include 30-40 patients with HL per year. More patients are expected to be included due to an extensive collaboration with centres outside the Netherlands within the European Network of Paediatric Hodgkin`s Lymphoma (EuroNet-PHL) community; we expect to include ~60-80 patients per year.
Sampling will be performed by trained research nurses and doctors after obtaining informed consent. All cases will be defined as cHL morphologically and immunohistochemically and classified into histologic subtypes by an hematopathologist. Whole exome sequencing of the malignant HRS cells will be

done in the laboratory of Prof. F. Holstege at the Princess Maxima Center, Utrecht. In newly diagnosed patients or in patients at relapse or at progression during treatment, immunohistochemistry for TARC will be performed to confirm expression of TARC by Hodgkin tumour cells. Subsequently, T-cell subpopulations, NK-cells, macrophages, PD-L1/ PD-1 expression and immune inhibitory cytokines such as IL1-10 and TGF will be examined on tissue samples. Serial serum samples will be measured at diagnosis (baseline) and at fixed time points during treatment and follow-up (see table 2,3 and 4 in the protocol). The biomarkers will be measured by Luminex® technology or by enzyme-linked immunosorbent assay (ELISA) performed by the Laboratory of Translational Immunology of the WKZ in Utrecht. Normal cytokine levels were defined on the basis of the ELISA kit purchasers instructions. In addition, serum samples are collected from age-matched healthy controls to define normal serum TARC levels in paediatric patients. Biomarker levels will be directly compared to PET-scans.cfDNA will be measured by different sequencing techniques and compared with whole genome sequencing results of sorted Hodgkin cells. This will be done at the research laboratory of Princess Máxima Center of Paediatric Oncology, Utrecht

Study burden and risks

There will be no extra burden or risk for the patients.
We will take blood samples of on fixed time points before, during and after treatment. In table 2,3 and 4 of the study protocol the exact time points are mentioned, this depends on the treatment level conform the EuroNet-PHL protocol. Blood samples will always be taken together with standard blood tests according to the protocol. Two extra tubes of blood will be collected for this research.
Moreover we will use some of the lymph node tissue that is taken out at diagnosis with the biopsy to investigate expression of the biomarkers. This changes nothing in the procedure of the biopsy.
For the control group, Two extra tubes of blood will be collected during the already planned necessary blood tests during their outpatient clinical visit.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

In order to be eligible to participate in the Hodgkin lymphoma group, a subject must meet all of the following criteria:

• Diagnosis of classical Hodgkin Lymphoma confirmed by reference pathology
• Patient aged below 18 at time of diagnosis
· Treatment according the European Network of Paediatric Hodgkin`s Lymphoma Second International Inter-Group Study for Classical Hodgkin*s Lymphoma in Children and Adolescents (EuroNet-PHL-C2) protocol or treatment for relapsed or refractory patients or according to the Open-label, Uncontrolled, Multicenter Phase II Trial of MK-3475 (Pembrolizumab) in Children and Young Adults with Newly Diagnosed Classical Hodgkin Lymphoma with Inadequate (Slow Early) Response to Frontline Chemotherapy.
• Written informed consent of the patient and/or the patient's parents or guardians according to national laws

Exclusion criteria

- HIV positivity
- Other underlying immunologic disorders causing an inadequate or overactive immune response, with the exception of Epstein Barr Virus

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-11-2016
Enrollment:	230
Type:	Actual

Ethics review

Approved WMO Date:	21-07-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	25-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 28180
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL52872.078.15