Iron chelation with Deferasirox under conditioning therapy prior to allogenic stem cell transplantation

Title

Iron chelation with Deferasirox under conditioning therapy prior to allogenic stem cell transplantation

Trial Description

Brief Summary in Lay Language

Patients with bone marrow malignancies often have chronic iron overload due to repeated blood transfusions, as erythrocyte concentrates also carry a considerable amount of iron. Chemotherapy - as it is necessary for example as a conditioning therapy before stem cell transplantation - results in an intended destruction of cells and thereby in many cases causes an acute release of iron (so called “labile plasma iron”) from the destroyed cells. The human body is not able to eliminate iron by itself and to compensate an iron overload. Acute or chronic iron overload can lead to organ damage. In addition, there is evidence that an iron overload favors the occurrence of infections.

The main purpose of this study is to investigate whether therapy with deferasirox (an approved drug used in chronic iron overload) can bind and eliminate the acute released labile plasma iron during conditioning therapy prior to stem cell transplantation. Furthermore, the tolerability of deferasirox in the context of conditioning therapy should be assessed. In addition, it should be investigated whether the treatment with deferasirox has an additional influence on the blood levels of busulfan (a chemotherapy commonly used in the conditioning therapy).

The dose of busulfan is routinely calculated for each patient individually based on measured blood levels as part of therapeutic drug monitoring (TDM).

Adult patients with chronic iron overload who will receive a stem cell transplant because of a malignant bone marrow disease and who are scheduled to receive busulfan as part of the conditioning therapy are eligible study participants. The presence of a chronic, transfusion-related iron overload can be determined by means of a laboratory value (ferritin).

From the beginning of the conditioning therapy, the study participants will receive the drug deferasirox (Exjade film-coated tablets) once daily until three days after the stem cell transplantation. To determine the effect of deferasirox on the occurrence of labile plasma iron during conditioning therapy labile plasma iron (LPI), serum iron, serum ferritin and transferrin (to calculate transferrin saturation) will be measured in the blood on days of conditioning chemotherapy and on days 4, 7 and 14 after stem cell transplantation. For this purpose, an additional blood sample (about 10 ml) will be taken from the central venous catheter during these days as part of the routine daily blood draw. The results of the blood tests will be combined with the clinical data (e.g. occurrence of side effects, occurrence of infections, occurrence of graft-versus-host reaction [GvHD], blood levels of busulfan and other medications, etc.) routinely collected during the therapy and evaluated with respect to the question set out above.
Patients with haematological diseases often suffer from anaemia, so repeated erythrocyte transfusions are necessary. This can cause a transfusion-related iron overload, which is associated with organ toxicity, increased susceptibility to infection and poorer prognosis. Additionally, in patients undergoing chemotherapy cellular iron is massively released due to the therapy-induced cell death. This results in a transient flooding of the iron transport routes and storage capacity, so that iron-specific, acutely toxic processes can take place. Iron overload can, on the one hand, directly, on the other hand via the generation of reactive oxygen species promote infections and graft-versus-host disease (GvHD) and ultimately lead via a chronic iron overload to damage of liver and heart, as well as to pancreatic and pituitary dysfunction, thus negatively impacting outcome in patients after allogeneic stem cell transplantation (allo-SCT).

Among the various markers of iron overload (e.g., serum ferric or liver iron), there are some conflicting results in terms of prognostic relevance. Iron release, measured as non-transferrin-bound iron (NTBI) during allo-SCT conditioning, is correlated with higher mortality and a higher rate of early infection. However, there is only a very weak correlation between NTBI and ferritin, so serum ferritin is not a meaningful parameter.

The study will evaluate whether deferasirox therapy in patients with chronic iron overload is capable of reducing the exposition of the patient with labile plasma iron (LPI) during conditioning therapy. Furthermore, the influence of deferasirox on the pharmacokinetics of busulfan, which is used in conditioning therapy, will be investigated. The tolerability of deferasirox during conditioning therapy prior to allogeneic stem cell transplantation and the impact on clinical outcome measures should be investigated as secondary targets.

Adult patients with an indication for allo-SCT and busulfan-containing conditioning chemotherapy as well as chronic transfusion-related iron overload (defined as serum ferritin > 1000 μg/L) are eligible for the study. Study participants will receive 14 mg/kg deferasirox as film-coated tablet (Exjade) once daily within the scope of the approved indication from the start of conditioning therapy up to day +3 after allogeneic stem cell transplantation. To assess the effect on the occurrence of labile plasma iron under conditioning, labile plasma iron (LPI), serum ferritin and transferrin saturation will be determined during all days of conditioning and on days +4, +7 and +14 after allogeneic stem cell transplantation. Potential effects of deferasirox on the pharmacokinetics of busulfan will be assessed by the routinely performed therapeutic drug monitoring (TDM). To assess the tolerability of deferasirox during conditioning therapy prior to allo-SCT, reported side effects as well as changes in laboratory parameters - classified according to the Common Terminology Criteria for Adverse Events (NIH / NCI) - will be used. The incidence of infections will be assessed by microbiological and clinical findings obtained during inpatient stay, considering bacteraemias (positive blood cultures) and invasive fungal infections (IFIs) - classified according to the EORTC criteria.

Do you plan to share individual participant data with other researchers?

[---]*

Description IPD sharing plan

[---]*
Organizational Data

- DRKS-ID: DRKS00015498
- Date of Registration in DRKS: 2018/10/10
- Date of Registration in Partner Registry or other Primary Registry: [---]*
- Investigator Sponsored/Initiated Trial (IST/IIT): yes
- Ethics Approval/Approval of the Ethics Committee: Approved
- (leading) Ethics Committee Nr.: PV5630, Ethik-Kommission der Ärztekammer Hamburg

Secondary IDs

- ICD10: E83.1 - Disorders of iron metabolism

Health condition or Problem studied

- Arm 1: Patients with chronic iron overload and a malignant haematological disease receive the iron chelator deferasirox as coated tablet once daily during conditioning therapy prior to allogeneic stem cell transplantation in a dosage of 14 mg/kg. Measurement of labile plasma iron and other iron metabolism parameters in the blood are performed during conditioning therapy before and on days 4, 7 and 14 after allogeneic stem cell transplantation.

Interventions/Observational Groups

- Study Type: Non-interventional
- Study Type Non-Interventional: Observational study
- Allocation: Single arm study
- Blinding: [---]*
- Who is blinded: [---]*
- Control: Uncontrolled/Single arm
- Purpose: Treatment
- Assignment: Single (group)
- Phase: N/A
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): No
**Primary Outcome**

1. Labile plasma iron (total exposure and maximum value) measured on all days of the conditioning therapy and on day +4, +7 and +14 after allogenic stem cell transplantation
2. Effect of Deferasirox on the pharmacokinetics of busulfan (therapeutic drug monitoring on the days of busulfan application)

**Secondary Outcome**

1. Tolerability of deferasirox according to CTCAE criteria
2. Combined endpoint of infection rates (bacteremia defined as positive blood cultures, invasive fungal infections according to EORTC criteria) until day 28 and toxicities grade IV NCI (CTCAE) until day 28 (bilirubin elevation, mucositis, acute renal failure)

**Countries of recruitment**

- DE Germany

**Locations of Recruitment**

- University Medical Center Universitätsklinikum Hamburg-Eppendorf, Hamburg
Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2018/11/30**
- Target Sample Size: **25**
- Monocenter/Multicenter trial: **Monocenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

chronic iron overload due to red blood transfusions (Ferritin ≥ 1000ng/ml), if a therapy with Deferoxamin is contraindicated or if inappropriate; Busulfan-containing conditioning therapy prior to allogenic stem cell transplantation

Exclusion criteria

- impaired kidney function (GFR < 60 ml/min), impaired liver function (≥ Child-Pugh B), concomitant therapy with drugs known as strong inductors of UGT (e.g. Phenytoin, Rifampicin, Phenobarbital, Ritonavir)
Addresses

- **Primary Sponsor**

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Sources of Monetary or Material Support

- Institutional budget, no external funding (budget of sponsor/PI)

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Status

- Recruitment Status: Recruiting complete, follow-up complete
- Reason, if "Recruitment stopped after recruiting started" or "Recruiting withdrawn before recruiting started": [---]*
- Reason, if Reason for Recruiting Stop "Other": [---]*
- Study Closing (LPLV): 2020/09/24
- Number of Participants in Germany after Recruiting complete: 25
- Total Number of Participants (all Sites worldwide) after Recruiting complete: 25

Trial Publications, Results and other documents

- trial protocol (mandatory for transfer to Studybox) Studienprotokoll Eisenchelation mit Deferasirox unter Konditionierung vor allogener Stammzelltransplantation

* This entry means the parameter is not applicable or has not been set.
*** This entry means that data is not displayed due to insufficient data privacy clearing.