Individualized dosing of fludarabine during innate allo SCT: A randomized phase II study

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Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON24753

Bron
Nationaal Trial Register

Verkorte titel
TARGET Study

Aandoening

Hematological malignancies, Allogeneic stem cell transplantation, personalized dosing of fludarabine

Ondersteuning

Primaire sponsor: University Medical Center Utrecht (UMCU)
Overige ondersteuning: University Medical Center Utrecht (UMCU)

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Cumulative incidence of severe viral infections at day 100

Toelichting onderzoek

Achtergrond van het onderzoek

Allogeneic stem cell transplantation (allo-SCT) is still the treatment of choice for many patients suffering from hematological malignancies, which can only occasionally be cured with conventional chemotherapy. Donor T cells contribute strongly to the beneficial effect of allo-SCT due to a potent graft versus leukemia effect after transplantation; however they also cause severe and life-threatening GVHD. In addition, relapses are frequently observed after allo-SCT. Recent reports have shown that the innate immune system can contribute to tumor control and control of infections, whereas the chance to induce GVHD appears to be low. Depletion of □□ T-cells prior to allo-SCT is therefore a valuable tool of discarding the potentially harmful T cells. Many different studies now indicate that □□ T-cell depletion in the graft reduces substantially life-threatening GVHD1-5. Also in the UMCU over 100 patients have received an αβ-T cell depleted allo-HSCT. In the outcome analyses of the first 75 patients we confirmed the low incidence of GVHD as suggested by multiple other reports 1-5. The cumulative incidence of severe III-IV aGVHD (0% at 3 months) and cGVHD (14%; 8% moderate/severe at 1Y) when utilizing an αβT cell depletion was markedly lower compared to our historical T cell replete cohorts. Low toxicity was also supported when analyzing the combined cumulative incidence of > grade III viral reactivations and aGVHD II-IV, which was 47% at 6 months. Event free survival and overall survival were at least comparable to T cell replete transplantations. Thus, the major benefit of αβT cell depletion comes in the short run from the early window of opportunity to add additional immune interventions as well as in the long run from the very low incidence of chronic GVHD. However, analyzing the outcome of αβT cell depletion transplantation cohorts in depth also defined a group of patients who suffer from viral complications. Though the incidence of severe viral complications was low when compared to other cohorts, a retrospective analysis suggests that in particular patients with too high fludarabine exposures had an increased chance of profound infection. Current guidelines to adapt for fludarabine exposures seem thus to be suboptimal and we developed based on our retrospective analysis of T cell replete and T cell deplete transplantation cohorts an algorithm which should allow an easy and more individualized dosing of fludarabine resulting in an optimized and equivalent fludarabine exposure across all patients. We hypothesize that a more personalized dosing of fludarabine will translate into a lower incidence of severe viral infections, while low incidence of GVHD remains. This would render more patients eligible to early post allo-SCT interventions. In order to test this hypothesis we will randomize in this protocol the individualized dosing of fludarabine against standard of care arm, which does use dosages based on current guidelines.

Doel van het onderzoek

Allogeneic stem cell transplantation (allo-SCT) is still the treatment of choice for many patients suffering from hematological malignancies, which can only occasionally be cured

with conventional chemotherapy. Allo-SCT still associates with a high transplant related morbidity and mortality. Fludarabine (FLU) is part of many regimens utilized for conditioning. Recent analysis of a retrospective allo-SCT patient cohort has shown that high exposure of FLU results in an increased risk of viral infections and subsequent change of non-relapse mortality.

With ‘individualized dosing of FLU’ we aim to reduce the change of overexposure to FLU, which to diminish the change of infectious complications.

Onderzoeksopzet

Primary endpoint: day 100

Secondary endpoints: Follow-up 1 year

Onderzoeksproduct en/of interventie

Patients will be randomized to either to standard dosing of fludarabine or individualized fludarabine dosing as part of a conditioning regimen, followed by an αβTCR / CD19 depleted transplantation.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Adults (> 18 years)

2. AML, MDS, ALL, CML, CLL, NHL, HL, or a myeloproliferative disease (MPD)

3. Indication for allo-SCT according to the policy of the local center

4. WHO performance status ≤ 2

5. Written informed consent

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1.Relapse of disease within 5 months after previous allo-SCT

2.Bilirubin and/or transaminases > 2.5 x normal value*

3.Creatinine clearance < 40 ml/min*

4.Cardiac dysfunction as defined by:

-Unstable angina or unstable cardiac arrhythmias

-NYHA classification > II (Appendix B)

-Cardiac symptoms and/or history of cardiac disease AND a cardiac ejection fraction < 45%

5.Active, uncontrolled infection

Onderzoeksopzet

Opzet

Type: Interventie onderzoek

Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	Geneesmiddel

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-06-2018
Aantal proefpersonen:	98
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Positief advies

Datum:	09-04-2018
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 55832
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL6940
NTR-old	NTR7136
CCMO	NL64877.041.18
OMON	NL-OMON55832

Resultaten