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

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON24753

Source
Nationaal Trial Register

Brief title
TARGET Study

Health condition

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

Sponsors and support

Primary sponsor: University Medical Center Utrecht (UMCU)
Source(s) of monetary or material Support: University Medical Center Utrecht (UMCU)

Intervention

Outcome measures

Primary outcome

Cumulative incidence of severe viral infections at day 100

Secondary outcome

-Non relapse mortality (NRM) at day 100

-aGVHD grade II-IV at day 100

-Donor engraftment (chimerism > 95%) at day 100

-Overall survival at day 100

-Cumulative incidence of relapse at day 100

-Effective fludarabine exposure

Study description

Background summary

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.

Study objective

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.

Study design

Primary endpoint: day 100

Secondary endpoints: Follow-up 1 year

Intervention

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.

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Eligibility criteria

Inclusion criteria

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

Exclusion criteria

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

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-06-2018
Enrollment:	98
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion

Date:	09-04-2018
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 55832
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

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

Study results