10-day decitabine, fludarabine and 2 Gray TBI as conditioning strategy for poor and very poor risk AML in CR1. PLMA34 study

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON40360

Source
ToetsingOnline

Brief title
Decitabine in the conditioning strategy for AML. PLMA34 study

Condition

- Leukaemias

Synonym
acute myeloid leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: Ministerie van OC&W,Johnson & Johnson Pharmaceutical

Intervention

Keyword: AML, conditioning, decitabine, HSCT

Outcome measures

Primary outcome

Primary endpoints:

* Relapse at 1-year after the transplantation procedure

* TRM at 1-year after the transplantation procedure

Secondary outcome

Secondary endpoints:

* Relapse within the first 100 days after the transplantation procedure

* TRM within the first 100 days after the transplantation procedure

* Grade II-IV and grade III-IV acute GVHD within the first year after the

transplantation procedure

* Chronic GVHD at 1 year after the transplantation procedure

* Rejection within the first year after the transplantation procedure

* Overall survival (OS) (based on intention to treat analysis)

* Disease free survival (DFS), event free survival (EFS)

* Cumulative incidence of relapse

* Days of staying in hospital and transfusion needs

* Evolution of donor T cell chimerism levels

* TNFR1, Il-8 and CRP peak and citrulline nadir on day +7 after transplantation

Study description

Background summary

Acute myeloid leukemia (AML) is a heterogeneous group of malignant hematological diseases with different molecular genetic abnormalities. These are important in predicting respons to treatment. Recently, an analysis of 424 AML patients treated in various HOVON protocols showed a 5 year overall survival for patients in good, intermediate, poor and very poor risk groups of 65%, 51%, 25% and 7% respectively (HOVON 102 protocol). This shows that especially for patients in the (very) poor risk group, the outcome is very disappointing, despite the current treatment strategies. For patients with intermediate, poor and very poor risk cytogenetics postconsolidation treatment with an allogeneic hematopoietic cell transplantation (allo HCT) is standard practice after myeloablative (MAB HCT) or non-myeloablative (NMA HCT) conditioning.
Unfortunately, mortality after MAB conditioning is still considerable, mainly due to therapy related mortality, graft-versus-host disease, infections, or relapse. Currently, the NMA conditioning is used more frequently, which is far less toxic. Nonmyeloablative regimens have relied on the immunological anti-leukemia effect (graft-versus-leukemia), to prevent relapsing disease. This anti-leukemia effect, however, needs time to develop, which makes it necessary to be in control over the disease pre-transplantation as much as possible. This extends the time the immune system of the donor has to develop an adequate anti-leukemia effect, which is especially important in the (very) poor risk group patients since they have the highest chance of relapse.

Epigenetic alterations are increasingly recognised for their roles in oncogenesis. These alterations can for example *silence*genes by hypermethylation. As these alterations are mainly outside the DNA itself, they are potentially reversible.
The hypomethylating agent decitabine is one of the therapeutic approaches which can reactivate silenced genes by its interaction on the epigenetics. A phase II study (Blum, Proc Natl Acad Sci 2010) with 53 AML patients who received 10 days decitabine, showed a complete remission rate (CR) in 47% of patients. This percentage corresponds to the CR of intensive chemotherapy in elderly AML patients. The disease free survival was 46 weeks. The median survival was 55 weeks. Furthermore, this study showed that decitabine was well tolerated. Despite a prolonged period of neutropenia, they did not develop a painful mucositis. Earlier studies have showed that hypomethylating agents pre-transplantation result in comparable survival as with toxic chemotherapy (Damaj, JCO 2012). In contrast to the discussed studies, which solely used hypomethylating agents to control the disease, in the current study the AML is already in remission after intensive chemotherapy. For this study, we want to add 10-day decitabine prior to NMA HCT by combining 10-day decitabine with the

Flu/TBI conditioning regimen in poor and very poor risk AML patients. The hypothesis is that in this way we can extent the time the immune system of the donor needs to create an adequate graft-versus-leukemia effect, at the cost of low toxicity.

Study objective

The primary objective of this study is to assess the feasibility (safety and efficacy) of addition of 10-day decitabine to the standard Seattle non-myeloablative conditioning regimen (3 days fludarabine 30 mg/m2 + 2 Gray TBI) prior to allogeneic HCT in poor and very poor risk AML patients in CR1. Safety will be assessed by adverse events and laboratory parameters; efficacy will be assessed by (decrease of) relapse rate at 15 months (fixed time point) after last-patient-in.

The secondary objectives of this study are:
1. To assess the safety profile: i.e. treatment related mortality (TRM) of the transplantation procedure and toxicity, associated with this conditioning regimen.
2. To assess transplant related parameters: i.e. acute and chronic graft-versus-host disease (GVHD), rejection, engraftment kinetics (T-cell and bone marrow chimerisms).
3. To assess the efficacy profile: i.e. relapse frequency after allogeneic HCT, overall survival (OS), disease free survival (DFS) and event free survival (EFS)
4. To assess the social/economic impact both therapy regimens: i.e. Quality of Life (QoL) (EORTC-Q30; t=0 and follow up), days staying in the hospital and transfusion needs.
5. To assess the impact of this conditioning regimen on mucositis (citrulline levels as biomarker of intestinal mucositis) and conditioning-induced inflammation (soluble TNFR1, IL-8 and C-reactive protein levels).

Study design

Multicenter, phase II intervention study

Intervention

The addition of 10 days (20 mg/m2) decitabine to the conditioningsregimen prior to allogeneic hematopoiectic transplantation.

Study burden and risks

There is an addition of the hospital stay of 21 days. The neutropenic period can be extended.

In this patient group, which consists of patients with (very) poor risk acute

myeloid leukemia, the chance of relapse is high despite current applied treatment strategies. In case of relapse, the risk of death is high. In our opinion it is very important to develop a strategy which lowers the risk of relapse in this patient category.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Patients (>17 yr) eligible for allogeneic HCT, independent of age
* Patients (>17 yr) with a cytopathologically confirmed diagnosis according to WHO classification of newly diagnosed AML (not APL <= AML-M3), de novo AML or secondary AML
* in first complete remission (CR1)
* Poor risk or very poor risk subgroups
* WHO performance status * 2

* Written informed consent;Poor risk is defined as:
- Normal karyotype, WBC * 100, not in CR after first cycle of chemo
- Normal karyotype, WBC > 100
- Abnormal karyotype, non CBF, MK, no abn 3q26, EVI1-;Very poor risk is defined as:
- Non CBF, MK+
- Non CBF, abn 3q26
- Non CBF, EVI1+
- Non CBF, high Flt3-ITD allelic burden ;CBF <= core binding factor
MK <= monosomal karyotype

Exclusion criteria

* Patient not in CR1
* Patients who have senile dementia, mental impairment of any other psychiatric disorder that prohibits the patient from understanding and giving informed consent
* Active serious infections like HIV, HBV and HCV
* Patient is unwilling to use contraceptive techniques during and for 12 months following treatment
* Female patient who is pregnant or breastfeeding

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-10-2014
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dacogen
Generic name:	decitabine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-06-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-09-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-01-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-000400-99-NL
CCMO	NL47271.091.14

Study results

Date completed: 07-05-2019

Actual enrolment: 53

Summary results
Trial is onging in other countries