A Randomized, Multi-Center Phase III Trial comparing two conditioning regimens (CloFluBu and BuCyMel) in children with Acute Myeloid Leukemia undergoing allogeneic stem cell transplantation.

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This study has been transitioned to CTIS with ID 2023-505512-37-00 check the CTIS register for the current data. The primary objective of the randomized part of the protocol is to investigate if a conditioning regimen containing one alkylator (Bu)...

Ethical review	Approved WMO
Status	Pending
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON53923

Source
ToetsingOnline

Brief title
SCRIPT-AML

Condition

- Leukaemias
- Leukaemias

Synonym
Acute Myeloid Leukemia (AML), blood cancer

Research involving
Human

Sponsors and support

Primary sponsor: Västra Götaland Regionen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Acute Myeloid Leukemia, Adolescents, Children, Stem cell transplantation

Outcome measures

Primary outcome

The primary end-point is a comparison of the 2-year acute grade III to IV-free,

chronic nonlimited GVHD-free, relapse-free survival (GRFS) between the 2 arms

of the trial. GRFS is defined as the time from randomization to the first event

(acute GvHD III-IV, chronic nonlimited GvHD, relapse, death) or last follow-up.

Secondary outcome

Exploratory endpoints in both interventional and observational parts of the

study:

- Disease free Survival (DFS)

- Overall Survival (OS)

- Cumulative incidence of relapse (CIR)

- Transplant-related Mortality (TRM)

- Hematologic Recovery

- Graft Failure (GF)

- Immunereconstitution

- Acute GVHD

- Chronic GVHD

- Infections

- Toxicity

Study description

Background summary

The role of conditioning regimen in allogeneic hematopoietic stem cell transplantation (HCT) of acute myeloid leukemia (AML) in pediatric patients is not well studied. Donor choice, graft source, type of conditioning regimen and intensity of GVHD prophylaxis can significantly impact both anti-leukemic efficacy and transplant related mortality (TRM), and the benefit of reduced incidence of relapse after HCT can be counterbalanced by an increased TRM rate. Historically, there have been two standard conditioning regimens for leukemia, namely regimens consisting of Busulfan and Cyclophosphamide or TBI and Cyclophosphamide. Relapse after HCT was mainly regarded as conditioning regimen failure. Therefore, the addition of a third alkylator (Melphalan) to a standard BuCy regimen was investigated.
Escalation of the intensity of a standard conditioning regimen by the addition of a third alkylating agent is associated with a high toxic burden for the patients.To find a less toxic conditioning regimen with potent antileukemic activity, the combination of Clofarabine, Fludarabine, and Busulfan (CloFluBu) was investigated.
BuCyMel had proven to be an efficacious conditioning regimen in allo-HCT for pediatric AML but comes with high toxicity. CloFluBu might be a less toxic alternative, with good anti-leukemic properties. This prospective randomized study will compare both conditioning regimens for the primary endpoint 2-year acute grade III to IV-free, chronic nonlimited GVHD-free, relapse free (GRFS).

Study objective

This study has been transitioned to CTIS with ID 2023-505512-37-00 check the CTIS register for the current data.

The primary objective of the randomized part of the protocol is to investigate if a conditioning regimen containing one alkylator (Bu) combined with two antimetabolites (Clo and Flu) results in superior 2-year acute grade III to IV-free, chronic non-mild GVHD-free, relapse-free survival than a conditioning regimen combining three alkylating agents (BuCyMel).

Exploratory objectives:
1) To compare the following outcomes between the 2 arms of the trial:
• neutrophil and platelet engraftment

• rate of primary and secondary graft failure
• cumulative incidence of relapse
• cumulative incidence of transplant-related mortality
• disease-free and overall survival
• incidence of grade II-IV and III-IV acute GVHD
• incidence of chronic GVHD
• rates of Grade >= 3 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, and specifically
o Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease (SOS/VOD)
o Engraftment Syndrome (ES)
o Transplant-associated thrombotic microangiopathy (TA-TMA)
o Hemorrhagic Cystitis (HC)
o Mucositis
• incidence of infections
• immunological recovery
• quality of life
• late effects
• nutritional status

2) To analyze the association between pre-HCT minimal residual disease in the last bone marrow sample taken before start of conditioning, and incidence of relapse, disease-free survival, and overall survival.

Study design

This study is composed of two parts - an interventional part that includes randomization, and an observational part. The interventional part is a phase III randomized, open label, multicenter parallel group trial comparing two conditioning regimens used in pediatric HCT: a three alkylator combination of busulfan, cyclophosphamide and melphalan (BuCyMel, standard arm) and a combination of clofarabine, fludarabine and busulfan in which two alkylators are replaced by antimetabolites (CloFluBu, experimental arm).
The primary outcome of 2-year acute grade III to IV-free, chronic non-limited GVHD-free, relapse-free survival (GRFS) will be compared between the two conditioning regimens.
The observational part will prospectively register outcome measures of transplantation in patients not fulfilling criteria for participation in the interventional part of the study (due to lack of complete remission, lack of matched sibling or unrelated donor, who were not recruited to a national upfront protocol or who decline participation in randomization) but consenting to registration of the data.

Intervention

Randomisation between 2 conditioning regimens:
1) BuCyMel, standard arm

2) CloFluBu, experimental arm

Study burden and risks

This trial studies the conditioning in search of the least toxic effective regimen. The additional burden on the participating patient is minimal, the significance for patients in the future is great. The additional bone marrow punctures are not perceived as a great burden by patients and parents. They often ask for it, to be informed about the status of the leukemia even after the transplantation, they are used to it during the leukemia treatment as well.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

Inclusion criteria for randomization part of the study:
• Age <=18 years at time of initial AML, age <= 21 years at transplantation.
• HCT is performed in a study participating center
• All women of childbearing potential who have to have a negative pregnancy test within 2 weeks prior to the start of treatment.
• Signed informed consent.
• Any relapsed AML after initial treatment according to a defined international AML protocol. (NOPHO-DBH AML 2012/new protocol), or AML in first remission with transplant indications and treatment according to national AML protocol (NOPHO-DBH AML 2012 or new protocol).
• In hematological remission, defined as
o < 5 % leukemic blasts confirmed by flow cytometry (in patients with an informative leukemia associated immunophenotype) in a bone marrow sample taken <=14 days prior to start of conditioning and
o no evidence of extramedullary disease, including in CNS and
o no leukemic blasts in the peripheral blood (verified by flow cytometry in case immature cells are detected in the peripheral blood differential).
• Patients must have a related or unrelated donor fulfilling any of the following criteria
o HLA 10/10 allelic matched, identical, sibling BM donor or
o HLA 10/10 or 9/10 allelic matched related/unrelated BM or PBSC donor or
o HLA 5-6/6 unrelated or 6-7-8/8 unrelated Cord Blood (UCB).

Inclusion criteria for observation/registration only:
• Diagnosis of acute myeloid leukemia
• Indication for allogeneic stem cell transplantation, as defined by primary treatment protocol or treating physician.
• Age <=18 years at time of initial AML, age <= 21 years at transplantation.
• Not eligible for randomization, either due to lack of consent or not fulfilling inclusion criteria for interventional part of the study.
• Signed informed consent to prospectively register follow-up data.

Exclusion criteria

Exclusion criteria for randomization part of the study:
• Diagnosis of juvenile myelomonocytic leukemia (JMML).
• History of previous malignancy (AML diagnosed as secondary cancer).
• Known diagnosis of Fanconi anemia.
• Prior autologous or allogeneic hematopoietic stem cell transplant.
• Planned prophylactic DLI or other immunotherapeutic interventions after HCT that are not included in the upfront protocol,
• Planned anti-leukemic medication after HCT that are not included in the

upfront protocol
• Known intolerance to any of the chemotherapeutic drugs in the protocol.
• Major organ failure precluding administration of planned chemotherapy.
• Patients with uncontrolled bacterial, viral, or fungal infections (currently taking medication and with progression or no clinical improvement) at time of enrollment.
• Severe concomitant disease that does not allow treatment according to the protocol at the investigator*s discretion, e.g. malformation syndromes, cardiac malformations, metabolic disorders, renal impairment (<30% of normal glomerular filtration rate), severe pulmonary, hepatic or cardiac impairment due to toxicity or infection.
• Karnofsky / Lansky score < 50%
• Females who are pregnant (positive serum or urine βHCG) or breastfeeding.
• Females of childbearing potential or men who have sexual contact with females of childbearing potential unwilling to use effective forms of birth control or abstinence for one year after transplantation.
• Subjects unwilling or unable to comply with the study procedures.

Exclusion criteria for observation/registration only:
• Diagnosis of Myelodysplastic syndrome (MDS).
• Diagnosis of Juvenile myelomonocytic leukemia (JMML).
• Age above 21 years at time of transplantation
• No consent is given to prospectively register outcome data
• Prior autologous or allogeneic hematopoietic stem cell transplant.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Pending

Start date (anticipated):	01-06-2023
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Busilvex
Generic name:	Busulfan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Clofarabine
Generic name:	Clofarabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Cyclophosphamide
Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Fludarabine
Generic name:	Fludarabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Melphalan
Generic name:	Melphalan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-02-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-04-2023

Application type:	First submission
Review commission:	METC NedMec

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
EU-CTR	CTIS2023-505512-37-00
EudraCT	EUCTR2021-003282-36-NL
CCMO	NL83430.041.23