Allogeneic Stem Cell Transplantation (SCT) for children and adolescents with acute lymphoblastic Leukaemia (ALL)

Published: 08-07-2014
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This study has been transitioned to CTIS with ID 2024-512657-24-00 check the CTIS register for the current data. Stratum 1:To show that a non total body irradiation (TBI) containing conditioning (Flu/Thio/ivBu) results in a non inferior survival as...

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

Summary

ID

NL-OMON54836

Source
ToetsingOnline

Brief title
ALL SCTped 2012 FORUM

Condition

- Leukaemias

Synonym
cancer of the blood, leukaemia

Research involving
Human

Sponsors and support

Primary sponsor: St, Anna Kinderkrebsforschung
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: children, conditioning, leukaemia, SCT

Outcome measures

Primary outcome

Stratum 1: Overall Survival (OS)

Stratum 2: Event Free Survival (EFS)

Secondary outcome

Stratum 1: EFS

Stratum 2: OS

Stratum 1 and 2:

• Cumulative Incidence of Treatment-related mortality (TRM)

• Cumulative Incidence of Relapse

• Toxicity: acute and late

• Acute Graft versus Host Disease (aGVHD) and chronic GVHD (cGvHD)

• Secondary malignancies

Study description

Background summary

Patients with high risk or relapsed acute lymphoblastic leukaemia (ALL) have a poor prognosis. For these patients intensive therapy is required after they have achieved remission with multimodal chemotherapy. Allogeneic hematopoietic stem cell transplantation (HSCT) can effectively induce immunological antileukaemic control in patients with ALL by means of the graft-versus-leukaemia effect (GvL), but treatment related mortality (TRM), morbidity and late effects remain serious problems of this treatment modality. In the last decade the short term outcome of children with ALL who received

allogeneic HSCT has improved, due to the use of donors more closely matched by Human leukocyte antigen (HLA) typing, resulting in less severe graft vs host disease (GvHD) and better supportive care. However, the risk of life long complications persists in all children.

In addition, the group of patients who do not identify a HLA compatible donor is still faced with a HR for life threatening transplantation associated complications. Therefore, this study attempts to explore the possibility, whether children with an indication for an allogeneic HSCT can benefit from omitting TBI and if children without a compatible donor could be successfully rescued with stem cell from alternative donors.

Update 21-MAY-2019: Interim analysis of this study showed a superior EFS and OS in the TBI/VP16 arm. Randomisation stopped. TB/VP16 is the standard treatment in The NL after this interim analysis.

Total Body Irradiation (TBI): for decades TBI has been the most frequently applied myeloablative and immunoablative procedure before HSCT in patients with ALL. Most centres use fractionated TBI to reduce acute side effects, such as nausea and vomiting, and late effects, such as cataracts. Lung shielding is also widely used to prevent severe non infectious pneumonitis. In Europe, most centres do not irradiate children below the age of 2 years due to the deleterious effects on the developing brain. However, the biggest burdens for children given TBI are the risks of secondary malignancies, growth retardation (especially if irradiated below 10 years) and infertility (most common after irradiation during or after puberty). To date, it has not been shown that TBI in the conditioning regimen for childhood ALL can be replaced by chemotherapy.

Etoposide (VP16): For many groups the standard chemotherapy conditioning was cyclophosphamide in combination with TBI. Dopfer et al. and the recent BFM- and BFM international studies have shown better results with a conditioning regimen consisting of TBI/VP16. Therefore, the comparator for the study questions consists of a conditioning with TBI/VP16 for children above 4 years.

Intravenous Busulfan (ivBU) in children:
IvBu is licensed for use in children and is the most common myeloablative chemoconditioning for paediatric HSCT in non malignant diseases. Since the availability of ivBu, numerous studies have demonstrated the safety, feasibility and engraftment efficacy in children with malignant and non malignant disease. Sanz et al have published their experience of using a combination of Bu, Flu and Thiotepa for patients with haematological malignancy. The doses are the basis of those used in this protocol.

Fludarabine (Flu):
Fludarabine, a purine analogue with potent antitumor and immunosuppressive activity, is a common component of conditioning regimens before allogeneic non myeloablative HSCT in children. Its immunosuppressive properties promote

engraftment, development of donor chimerism and GvL effects.

Thiotepa
Thiotepa is a bialkylating highly lipid soluble agent with both myeloablative and immunosuppressive activity in haematological malignant disease. Apart from its use at high doses for patients with CNS tumours, it has been widely used as an additional agent to promote engraftment in allogeneic transplantation for a variety of non-malignant condition and also to promote the anti-leukaemic efficacy in TBI-based regimens. Most recently, it* use has been reported in combination with Bu and Flu for patients with malignancy (Sanz).

Study objective

This study has been transitioned to CTIS with ID 2024-512657-24-00 check the CTIS register for the current data.

Stratum 1:
To show that a non total body irradiation (TBI) containing conditioning (Flu/Thio/ivBu) results in a non inferior survival as compared to conditioning with TBI/Etoposide in children older than 4 years after HSCT from a Human leucocyte antigen (HLA) identical sibling donor (MSD) or a HLA matched donor (MD).
Update 21-05-2019: randomisation related question was closed in December 2018; patients are in active follow-up:

Update 21-05-2019:
Stratum 1 - MSD/MD: To explore the impact of risk factors on the incidence of adverse events of special interest (AESIs) and on overall survival and event free survival in the entire MSD/MD cohort (question 3 and 5) .

Stratum 2:
To explore event free survival (EFS) after HSCT from HLA mismatched donors using mismatched unrelated donors (MMD), mismatched cord blood or HLA haplo-identical family.

Study design

Update 21-05-2019: Randomisatie closed. Participants receive standard treatment, registration of treatment, outcome, toxicity and late effects.

The ALL SCTped 2012 FORUM is a multinational, multi-centre, randomized, controlled, prospective phase III study for the therapy and therapy optimisation for children and adolescents with ALL in complete remission, who have an indication for Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) with a myeloablative conditioning regimen.

The stratification and randomisation of patients in first and following remission according to the individual transplantation modalities rests upon an indication for allogeneic HSCT AND on the availability of a suitable donor within the individual transplantation groups.

Randomisation will be performed in the web-based study database.
Eligibility for randomisation (to TBI or not) is as follows:
• Fullfills all study entry criteria, including signed informed consent for randomisation
• Age 48 months or more (Less than 48 months - chemo arm only)
• Donor is MSD or MD donor (MMD -non-randomly allocated to chemo arm)
• Past cranial irradiation exposure is either:
18Gy or less if more than 24 months ago
12Gy or less if less than 24 months ago
• No active CNS disease
• No ALL with extramedullary involvement with indication for TBI
• No Trisomy 21

In case of refusal of the randomisation the patient is treated according to the standard arm (i.e. TBI/VP16).

Intervention

A conditioning regimen is mandatory in all cases; this protocol studies the way of conditioning.

Study burden and risks

Acute and late side effects of TBI in combination with VP16 are manifold to the growing organism and include severe organ dysfunction/failure due to toxicity. Although transplant associated mortality was reduced after HSCT in the last decade due to better HLA matching, infection prevention and control, the burden of late complications is still a matter of concern. Growth retardation, hormonal dysfunction, sterility and the risk of secondary cancer are the late consequences of TBI in children. However, so far no prospective study has demonstrated similar outcomes in paediatric ALL using chemo-conditioning regimen before HSCT. Therefore, this study aims to explore the efficacy and efficiency of a chemo-conditioning regimen (Flu/Thio with ivBu) in comparison to the standard conditioning regimen (TBI/VP16). The potential benefit for children and adolescent not receiving TBI are less severe acute organ toxicity due to reduced inflammation processes, less severe gonadal damage and especially a reduced risk for secondary malignancies. The potential risk for patients not receiving TBI for a highly aggressive leukaemia is relapse after HSCT. However, we anticipate an immunological disease control by the graft as most of the patients will receive non T-cell depleted transplants. In addition, there will be a chance for patients relapsing after a chemotherapy conditioning

to receive TBI prior to a second allograft. Although all components of the chemoconditioning have been used for years in children undergoing HSCT, the combination of Flu/Thio/ivBu have not been explored in larger trials for paediatric ALL and side effects have to be carefully followed.

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

Patients with ALL (except for patients with mature B-ALL) who fulfil the following criteria:
• Age at diagnosis <= 18 years or age at HSCT <= 21 years.

• indication for allogeneic HSCT
• complete remission (CR) before SCT
• written consent of the parents (legal guardian) and, if necessary, the minor patient via *Informed Consent Form*
• no pregnancy
• no secondary malignancy
• no previous HSCT
• HSCT is performed in a study participating centre

Exclusion criteria

• Patients who do not fulfil the inclusion criteria
• Non Hodgkin-Lymphoma
• The whole protocol or essential parts are declined either by patient himself/herself or the respective legal guardian
• No consent is given for saving and propagation of anonymous medical data for study reasons
• 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)
• Karnofsky / Lansky score < 50%
• Subjects unwilling or unable to comply with the study procedures

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	12-10-2016
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Busilvex
Generic name:	Busulfan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cyclophosphamide
Generic name:	Cyclofosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Etopophos 100mg Powder for Solution for Injection
Generic name:	Etopophos
Product type:	Medicine
Brand name:	Fludara
Generic name:	Fludarabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tepadina
Generic name:	Thiotepa
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-07-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-08-2014

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	05-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-05-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-04-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	CTIS2024-512657-24-00
EudraCT	EUCTR2012-003032-22-NL
ClinicalTrials.gov	NCT01949129
CCMO	NL45280.078.13