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A comparison of two low-intensity transplant regimens for the treatment of adults with acute lymphoblastic leukaemia (ALL) over the age of 40 years (ALL-RIC trial)

Submission date
08/01/2019

Recruitment status
No longer recruiting

Registration date
25/01/2019

Overall study status
Ongoing

Last Edited
06/06/2024

Condition category
Cancer

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol
Available at: https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-comparing-treatments-for-acute-lymphoblastic-leukaemia-all-ric

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Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2017-004800-23

ClinicalTrials.gov (NCT)
NCT03821610

Protocol serial number
38207; RG_17_241

Study information

Scientific Title
A comparison of reduced dose total body irradiation (TBI) and cyclophosphamide with fludarabine and melphalan reduced intensity conditioning in adults with acute lymphoblastic leukaemia (ALL) in complete remission

Acronym
ALL-RIC

Study objectives
The UKALL XIV trial has prospectively studied reduced intensity conditioning (RIC) transplants in adults with acute lymphoblastic leukaemia (ALL) in first remission over 40 years of age. Given this group had 15-20% survival in the previous UKALL XII trial, the 56% 2 year disease-free-survival (DFS) is encouraging. However, relapse at 2 years is high at 27%, especially in patients who come to transplant minimal residual disease (MRD) positive. Previous studies suggested that total body irradiation (TBI) conditioning in patients who received full intensity or RIC transplants reduced treatment failure (OR 1.4). The trialists propose to compare the two conditioning regimens and postulate that total body irradiation (TBI) 8Gy and cyclophosphamide 100mg/kg will be well tolerated and will reduce relapse. Experience from the German group with 8Gy TBI and in the SCOT trial suggests that this regimen is well tolerated with minimal extramedullary toxicity and low transplant related mortality (TRM).

Ethics approval required
Old ethics approval format

Ethics approval(s)
East Midlands - Leicester Central Research Ethics Committee, The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, Tel: +44 (0)207 104 8098; Email: nrescommittee.eastmidlands-leicestercentral@nhs.net, 12/06/2018, ref: 18/EM/0112

Study design
Randomised; Interventional; Design type: Treatment, Drug, Radiotherapy

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute lymphoblastic leukaemia

Interventions
This is a two-arm phase II, multicentre, randomised clinical trial comparing the outcome of patients transplanted using a TBI and cyclophosphamide allograft with patients transplanted with a FMA conditioning regimen. Patients with ALL who fulfil the eligibility criteria will be invited to participate in the trial across UK centres performing allogeneic SCT.

Patients will be randomised to treatment based on a minimisation algorithm prepared at the Cancer Research UK Clinical Trials Unit (CRCTU). Minimisation will be based upon age (>55; <55 years) and by donor type (sibling; unrelated).

Active Comparator: Fludarabine / Melphalan / Alemtuzumab
Day -7: Fludarabine 30 mg/m2 od IV
Day -6: Fludarabine 30 mg/m2 od IV
Day -5: Fludarabine 30 mg/m2 od IV
Day -4: Fludarabine 30 mg/m2 od IV
Day -3: Fludarabine 30 mg/m2 od IV
Day -2: Melphalan 140 mg/m2 od IV, Alemtuzumab 30 mg od IV (unrelated transplants only)
Day -1: Alemtuzumab 30 mg od IV
Day 0: Infusion of sibling or unrelated donor peripheral blood stem cells

Experimental: Cyclophosphamide / TBI (8 Gy)
Day -6: Cyclophosphamide 50 mg/kg od IV , Mesna 20 mg/kg od IV, Mesna 76 mg/kg od IV
Day -5: Cyclophosphamide 50 mg/kg od IV, Mesna 20 mg/kg od IV, Mesna 76 mg/kg od IV
Day -4: Rest
Day -3: TBI (2 Gy) bd
Day -2: TBI (2 Gy) bd, Alemtuzumab 30 mg od IV (unrelated transplants only)
Day -1: Alemtuzumab 30 mg od IV
Day 0: Infusion of sibling or unrelated donor peripheral blood stem cells or bone marrow

Patients will be followed-up for a minimum of 5 years from the date of randomisation.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)

Fludarabine, melphalan, alemtuzumab, cyclophosphamide, mesna

Primary outcome(s)
Disease Free Survival (DFS) defined as time from randomisation to the first of relapse or death from any cause. Patients who are still alive and progression free at the end of the trial will be censored at the date they were last known to be alive. Bone marrow assessments carried out to assess disease status at baseline, Day 100, Month 6/9/12/15/18/21/24/30/36

Key secondary outcome(s))
1. Overall Survival defined as time from randomisation to date of death from any cause. Patients who are alive at the end of the trial will be censored at their date last known to be alive. Information will be captured on a Death Form Case Report Form (CRF).
2. Cumulative Incidence of Relapse (CIR) defined as time from randomisation to the date of relapse. Patients who die without relapse will be treated as a competing risk and patients who are alive and relapse free at the end of the trial will be censored as their date last seen
3. Non Relapse Mortality (NRM) defined as time from randomisation to death from any cause that occurred without relapse. Patients who relapse will be treated as a competing risk and patients who are still alive and relapse free at the end of the trial will be censored at their date last known to be alive. Incidence of Grade 2-4 acute GvHD within 100 days of transplant. GvHD should be assessed continuously throughout the trial according to Glucksberg Criteria (see Appendix 4 of protocol)
4. Incidence of chronic GvHD of any grade at 2 years. See above.
5. Occurrence and severity of VOD in the first 100 days, captured on a specific Veno-Occlusive Disease CRF (which is based on the new EBMT criteria for SOS/VOD diagnosis in adults). All post-transplant events of VOD should be reported as a SAE irrespective of how long after IMP has been administered.
6. Duration of hospitalisation recorded on Hospitalisation Form CRF between start of conditioning regimen and 1 year post transplantation
7. Quality of life assessed using SF36 and FACT-BMT at baseline, 3 months, 12 months and years 2, 3, 4 and 5
8. Full donor chimerism recorded at day 100 follow up
9. Occurrence and severity of TBI-related symptomatic pulmonary toxicity in the first 12 months. Assessed using: Forced Expiratory Volume (FEV) 1 (%), Forced Vital Capacity (FVC) (%), % of predicted Peak Expiratory Flow Rate (PEFR), corrected for HL (%), Single Breath diffusing capacity of the lungs for carbon monoxide (DLCO) (%)

Exploratory outcome measures:
1. Correlation of multi-lineage chimerism and relapse
2. Correlation of MRD with relapse. There is a specific MRD CRF
Cumulative incidence of relapse will be assessed by both MRD and multi-lineage chimerism using cumulative incidence curves and multivariable cox models. Analysis will be conducted when patients have been followed up for 2 years

Completion date
22/11/2027

Eligibility

Key inclusion criteria
Patients with morphologically documented ALL who meet the following criteria;
1. Patients between the ages of 40-65 years. NB: Patients under the age of 40 who are

considered unsuitable for a myeloablative transplant may enrol onto the trial following discussion with the CI via the Trials Office
2. Patients with ALL in first CR
3. Availability of a human leukocyte antigen (HLA) identical sibling or suitable matched unrelated donor (suitable matched defined as no greater than a single allele mismatch at HLA A, B, C or DRβ1). A single allele mismatch is permitted if there are adverse cytogenetics or MRD positivity at any timepoint
4. Patients considered suitable to undergo a RIC allogeneic SCT as clinically judged by the Local Investigator including:
4.1. Adequate hepatic and renal function as determined by full blood count and biochemistry assessment
4.2. Resolution of any toxic effects of prior therapy (including radiotherapy, chemotherapy or surgical procedures). Patients with bone marrow suppression following therapy may enter the trial
4.3. Patients with abnormal cardiac and/or pulmonary function must be considered fit for allogeneic SCT including 8Gy of TBI at the time of randomisation.
5. Patients with an ECOG performance status 0,1 or 2
6. Female of and male patients of reproductive potential(i.e. not post-menopausal or surgically sterilised) must use appropriate, highly effective, contraception from the point of admission for transplant conditioning therapy until 12 months after transplant
7. Patients have given written informed consent
8. Patients willing and able to comply with scheduled study visits and laboratory tests

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
102

Key exclusion criteria
1. Patients with contraindications to receiving RIC allogeneic SCT
2. Female patients who are pregnant or breastfeeding. All women of childbearing potential (WOCBP) must have a negative pregnancy test before commencing treatment
3. Adults of reproductive potential not willing to use appropriate, effective, contraception during the specified period
4. Patients with renal or hepatic impairment as clinically judged by Local Investigator
5. Patients with active infection, HIV-positive or chronic active Hep-A or -C
6. Patients with concurrent active malignancy. Patients with a previous history of malignancy can be included if that malignancy is considered to be at a low risk of recurrence

Date of first enrolment
22/11/2018

Date of final enrolment
22/11/2022

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
NHS Greater Glasgow and Clyde
Department of Haematology
1053 Great Western Road
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Study participating centre
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Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type

Charity

Funder Name
IMPACT Partnership - Leuka, Anthony Nolan, BSBMT

Results and Publications

Individual participant data (IPD) sharing plan
Trial data will be made available through the EU portal at the end of the trial.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		01/06/2023	02/06/2023	Yes	No
HRA research summary			28/06/2023	No	No