

ALL-RIC trial protocol

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BMJ Open ALL-RIC trial protocol: 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

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ABSTRACT

Introduction The usage of a T-cell depleted, reduced intensity conditioning (RIC) approach to haematopoietic cell transplantation (HCT) in adult patients with acute lymphoblastic leukaemia (ALL) over 40 years of age and in first complete remission (CR) has resulted in encouraging rates of event-free and overall survival in a population of adults with high risk disease. However, relapse rates remain high—with disease progression being the major cause of treatment failure. Using different, more powerful conditioning approaches is the logical next step in examining the role of RIC allogeneic HCT in adult ALL.

Methods and analysis The ALL-RIC trial is a two-arm, phase II, multicentre, randomised clinical trial in adult patients with ALL in first or second CR, who are undergoing allogeneic HCT. Comparison of a novel RIC transplant conditioning regimen using reduced-dose total body irradiation (TBI), cyclophosphamide and alemtuzumab, is made against a standardised RIC approach using fludarabine, melphalan and alemtuzumab. The primary outcome of the study is disease-free survival at 3 years, defined as time from randomisation to the first of either relapse or death from any cause. Patients who are still alive and progression-free at the end of the trial will be censored at their last date known to be alive. Secondary outcomes include overall survival and non-relapse mortality.

Ethics and dissemination The protocol was approved by the East Midlands—Leicester Central Research Ethics committee (18/EM/0112). Initial approval was received on 12 June 2018. Current protocol version (V6.0) approval obtained on 18 November 2019. The Medicines and Healthcare products Regulatory Agency (MHRA) also approved all protocol versions. The results of this trial will be disseminated through national and international presentations and peer-reviewed publications.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The trial aims to extend our knowledge of reduced intensity conditioning allografts in adult acute lymphoblastic leukaemia; it builds on the largest prospective trial of this therapeutic modality in UKALL 14.
- ⇒ The trial aims to improve outcomes in a rare haematological disease, in an older age group.
- ⇒ A limitation is that the trial is not powered to detect differences in longer-term complications such as second cancers.

Trial registration number EudraCT Number: 2017-004800-23.
ISRCTN99927695.

INTRODUCTION

The UKALL 14^{1 2} trial prospectively studied reduced intensity conditioning (RIC) transplantation in adults with high risk acute lymphoblastic leukaemia (ALL) in complete remission (CR)1 over 40 years of age, in an attempt to improve the poor outcomes seen with chemotherapy and the excessive transplant-related mortality (TRM) demonstrated with full intensity allogeneic haematopoietic cell transplantation (HCT) in this age group. The 55% 4-year event-free survival (EFS) on UKALL 14 is encouraging. However, relapse at 4 years is high at 33.6%, and is higher in patients who come to transplant with detectable minimal residual disease (MRD). Previous studies³ have suggested that

total body irradiation (TBI) conditioning in patients who received full intensity or RIC transplants can reduce rates of treatment failure (OR 1.4).³ The ALL-RIC trial aims to compare two RIC regimens, and postulates that 8Gy TBI in combination with cyclophosphamide 100mg/kg will be well tolerated and will be a more efficacious regimen in terms of reducing relapse as compared with a non-TBI containing RIC approach. Existing transplant data from other disease groups⁴⁵ suggests that 8Gy TBI is well tolerated with minimal extramedullary toxicity and low TRM.

Any patient with ALL with an indication for allogeneic HCT in first or second CR >40 years of age will be eligible for consideration for the ALL-RIC transplant study, as will patients <40 years of age who are deemed to be unfit for myeloablative conditioning approaches. Within the context of the preceding UKALL 14 trial, approximately 500 newly-diagnosed patients with ALL >40 years of age were recruited over the course of the study duration, with 236 RIC transplants being performed in patients in this age group. Initial recruitment predictions for the ALL-RIC study were based around an expectation that similar numbers of patients would meet the eligibility criteria for allogeneic HCT in the context of this study. Patients >40 years of age who do not have a sibling or well-matched unrelated donor available, who declined the option of allogeneic HCT or who have significant comorbidities/impaired performance status may not be considered for an RIC allograft on this trial.

The last two trials performed by the National Cancer Research Institute (NCRI) ALL group (UKALL 12 and 14) are considered world leading and have changed management of this challenging disease in the UK. The ALL-RIC trial hypothesises that by evaluating carefully considered, more potent conditioning RIC protocols as a strategy to reduce the risk of disease relapse after HCT without a concomitant increase in treatment-related toxicity, that rates of post-allograft relapse can be reduced and consequently that the outcomes for adults with high-risk disease can be further improved. This is the logical next step in examining the role of transplantation in adult ALL. In addition, the ALL-RIC trial would become the largest randomised controlled trial (RCT) to prospectively evaluate transplant conditioning regimens in ALL.

METHODS AND ANALYSIS

Study design

The ALL-RIC trial is a two-arm phase II, multicentre, RCT comparing the outcome of patients transplanted using a 8Gy TBI, cyclophosphamide and alemtuzumab conditioning approach to allogeneic HCT, with patients transplanted using a fludarabine, melphalan and alemtuzumab conditioning regimen (figure 1 (trial schema)). Patients with ALL who fulfil the eligibility criteria will be invited to participate in the trial across UK centres performing allogeneic HCT.

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 on age (>55; ≤55 years), donor type (sibling; unrelated) and CR status (CR1; CR2).

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

Patient and public involvement

From its inception, the ALL-RIC trial was co-developed with the patient and public involvement group based in the Cancer Research Clinical Trials Unit at the University of Birmingham and the NCRI ALL group. The group refined the protocol and participant-facing documents and provided input into the design.

Inclusion and exclusion criteria

Patients between the ages of 40–70 years (patients under the age of 40 who are considered unsuitable for a myeloablative transplant may enrol), patients with ALL in first or second CR, availability of a human leucocyte antigen (HLA) identical sibling or suitable matched donor, considered suitable to undergo an RIC allogeneic Stem Cell Transplant (SCT). Patients with an ECOG (Eastern Cooperative Oncology Group) performance status 0, 1 or 2, females of and male patients of reproductive potential must use appropriate, highly effective contraception until 12 months after transplant, given written informed consent, patients willing and able to comply with scheduled study visits and laboratory tests. Exclusion criteria include patients with contraindications to receiving RIC allogeneic SCT, female patients who are pregnant or breast feeding, all women of childbearing potential must have a negative pregnancy test before commencing treatment, adults of reproductive potential not willing to use appropriate, effective contraception during the specified period, with renal or hepatic impairment, with active, HIV-positive or chronic hepatitis A or C, with concurrent active malignancy and previous exposure to a high dose of radiotherapy. Some patients will have borderline pulmonary and/or cardiac function for receiving TBI; investigators were invited to discuss these patients with the chief investigator.

Consent

Patients will be identified as per-site established processes. Each eligible patient will be given a patient information sheet (PIS) to read more about the trial. The investigator will ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient. The right of the patient to refuse to participate in the trial without giving explanation will be respected.

Informed consent is requested from the patient by the investigator who has been delegated the responsibility on the delegation log.

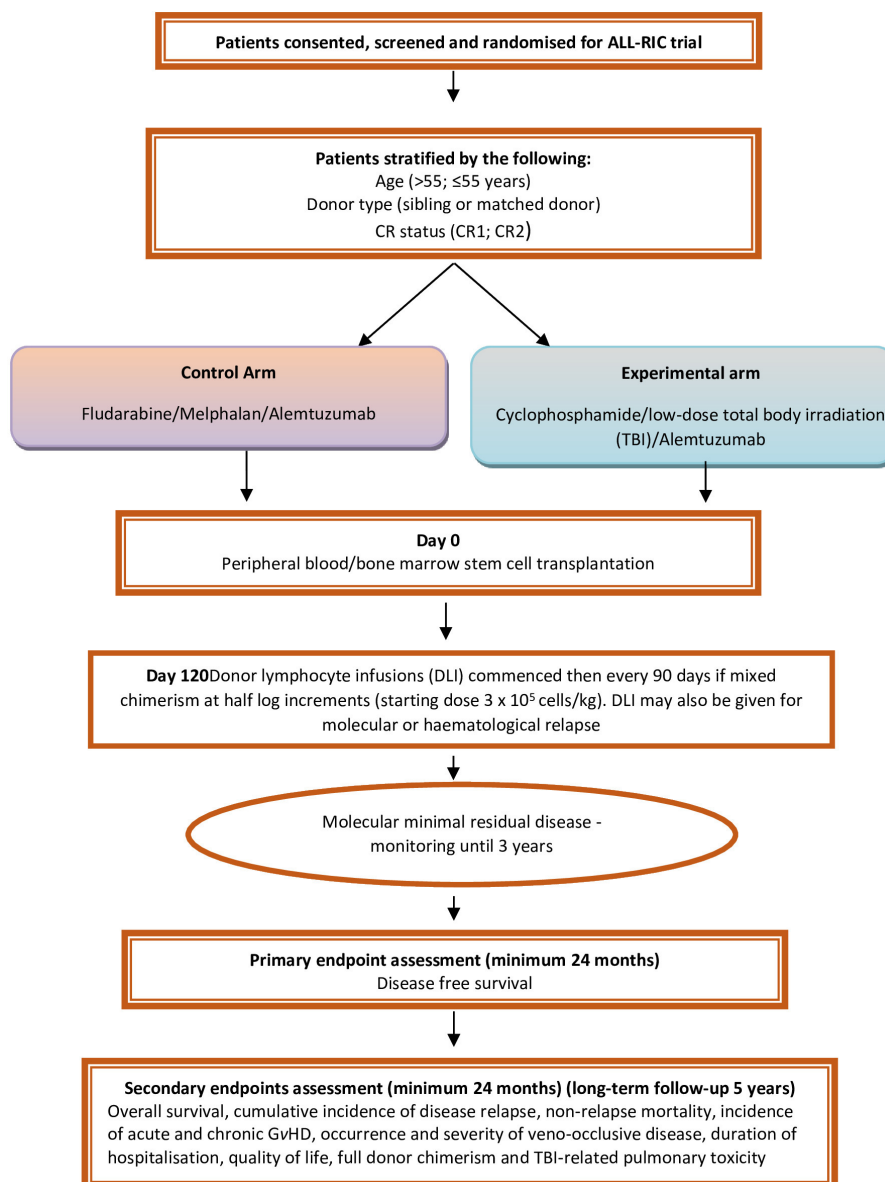


Figure 1 Trial schema. CR, complete remission; GvHD, graft versus host disease; TBI, total body irradiation.

Interventions

Control arm: fludarabine/melphalan/alemtuzumab

Fludarabine 30 mg/m² × 5 days, melphalan 140 mg/m² × 1 day, unrelated transplants only alemtuzumab 20 mg × 2 days, sibling transplants alemtuzumab 30 mg × 1 day.

Experimental arm: cyclophosphamide/TBI (8 Gy)

Cyclophosphamide 50 mg/kg × 2 days, mesna 20 mg/kg × 2 days and 76 mg/kg × 2 days, TBI 2 Gy two times a day × 2 days, unrelated transplants only alemtuzumab 20 mg × 2 days, sibling transplants alemtuzumab 30 mg × 1 day.

All patients will receive 12.5 mg intrathecal methotrexate every 3 months for 2 years post-transplant.

All patients will be given ciclosporin graft versus host disease (GvHD) prophylaxis according to local policy and levels should be monitored according to local practice. Supportive care including antimicrobial prophylaxis regimens are permitted according to institutional guidelines.

In addition to routine post-transplant visits all patients will be formally reviewed at day+100 and then every 3 months until month 60. Bone marrow aspirate pretransplant to confirm disease status, and then at day+100 and then every 3 months until month 36, with recommended molecular minimal residual disease monitoring at each time point.

Donor lymphocyte infusions will be administered at day 120 in both experimental and control arms in patients with a mixed T-cell chimerism or detectable MRD. The schedule will be: 120 days 3 × 10⁵ CD3+ cells/kg; 7 months 1 × 10⁶ cells; 10 months 3 × 10⁶ cells; 13 months 1 × 10⁷ cells and 16 months 3 × 10⁷.

Trial outcomes

The primary outcome is disease-free survival (DFS) which is defined as time from randomisation to the date of first relapse or death from any cause. Patients who are still

alive and progression-free at the end of the trial will be censored at their last date known to be alive.

The secondary outcomes are described below. The major secondary outcome is overall survival (OS) defined as time 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. Cumulative incidence of relapse 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. 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. Incidence of chronic GvHD of any grade at 2 years (investigator assessed using the Shulman criteria). Occurrence and severity of veno-occlusive disease in the first 100 days. Duration of hospitalisation recorded between start of conditioning regimen and 1-year post transplantation. Quality of life assessments including Short Form Health Survey (SF36) and Functional Assessment of Cancer Therapy - Bone Marrow Transplantation (FACT-BMT) collected at baseline, 3 months, 12 months and years 2, 3, 4 and 5. Full donor chimerism recorded at day 100 follow-up. Occurrence and severity of TBI-related symptomatic pulmonary toxicity in the first 12 months.

Statistical analysis plan

The main analysis of the data will take place once all the patients have completed 2 years of follow-up. A subsequent analysis of long terms outcome will be completed when all patients have completed 5 years of follow-up. All analysis in the trial will be conducted on an intention-to-treat population with the exception of safety analysis which will be evaluated on a per-protocol population. Sensitivity analysis of the primary outcomes will be conducted on a per-protocol population.

The primary outcome is DFS and will be calculated and presented using methods of Kaplan and Meier. A power analysis assumed that the experimental arm would improve DFS at 2 years by 15%. A sample size of 242 patients has a 80% chance of detecting a 15% difference with an alpha of 0.05. A Cox regression model will be used to compare between treatment arms. The model will include a treatment effect variables alongside variable to represent the stratification factors of donor type, CR status and age. A detailed secondary outcome measure analysis can be found in the Statistical Analysis Plan (online supplemental appendix 1).

Adverse events reporting and analysis

The collection and reporting of adverse events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments.

Only AEs that are equal to or greater than Grade 3 of the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0 will be reported. The reporting period for AEs will be from the date of commencement of protocol defined treatment until 100 days after the administration of the last treatment (Investigational Medicinal Product (IMP)). The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the Summary of Product Characteristics (SmPCs). Abnormal laboratory findings will only be reported if; (1) results in early discontinuation from the study treatment; (2) requires study drug dose modification or interruption, any other therapeutic intervention or is judged to be of significant clinical importance. Pre-existing conditions should only be reported if the condition worsens by at least 1 CTCAE grade. Hospitalisations for protocol defined treatment (including admission for transplant) or preplanned elective procedures unless the condition worsens will not be reported as serious (S)AEs.

Data management

Data will be collected via a set of forms capturing details of eligibility, baseline characteristics, treatment and outcome details. This trial will use an electronic remote data capturing system, with the exception of SAE reporting and pregnancy notification; both of which will be paper based. All trial records must be archived and securely retained for at least 25 years. No documents will be destroyed without prior approval from the sponsor, via the central ALL-RIC trial Office. On-site monitoring will be carried out as required following a risk assessment and as documented in the Quality Management Plan. Any monitoring activities will be reported to the ALL-RIC trial Office and any issues noted will be followed up to resolution. ALL-RIC will also be centrally monitored, which may trigger additional on-site monitoring. Further information regarding data management is provided in the study protocol.

Trial organisation structure

The University of Birmingham will act as a single sponsor for this multicentre study. The trial is being conducted under the auspices of the CRCTU, University of Birmingham, and in close partnership with The Adult ALL MRD Laboratory UCL Cancer Institute.

The trial management group (TMG) is responsible for the day to day running and management of the trial. Members include the Chief Investigator, Deputy Chief Investigator, Co-Investigators, Trial Statisticians, Trial Management Team Leader and Trial Coordinator. The TMG reports to the trial steering committee (TSC).

The TSC provides oversight and governance. Members include independent clinicians, members of the TMG and the CRCTU trial management team leader. Other members/observers may be invited if appropriate. The TSC supervises the conduct of the trial monitoring progress including recruitment, data completeness and

deviations from the protocol. They will make recommendations about conduct and continuation of the trial.

The independent data monitoring committee (DMC) includes clinicians and a statistician who will review unblinded data analyses to advise the TSC on whether trial data justified the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based on the template created by the Damocles Group. During the recruitment phase of the trial the DMC is scheduled to meet once 10 patients have been treated on the experimental arm to review early safety data. Subsequent meetings will be held annually thereafter. These may occur more frequently if the DMC deem necessary due to speed of recruitment or safety issues. The funding source (online supplemental appendix 2) had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data or decision to submit results.

Confidentiality statement

Confidential trial data will be stored in accordance with the General Data Protection Regulation 2018. As specified in the patient information sheet and with the patient's consent, patients will be identified using only their date of birth and unique trial ID number.

Trial status

Recruitment for the trial opened in September 2018 and will close on 30 September 2022.

DISCUSSION

Allogeneic transplantation has an established role in the management of patients with high risk ALL. While myeloablative conditioning approaches have been shown to reduce relapse rates in selected high risk patient populations, significant rates of non-relapse mortality in adult patients >35 years of age have been shown to negate the survival benefit that a reduction in relapse risk confers.⁶ Reduced-intensity conditioning has been evaluated in an attempt to exploit a graft versus leukaemia effect with reduced toxicity, with the UKALL 14 trial being the first study to prospectively evaluate the role of RIC allogeneic HCT in adult patients with ALL >40 years of age, using a T-cell deplete fludarabine, melphalan and alemtuzumab (FMA) approach to conditioning. The trial constituted the largest series of RIC allografts for older patients with ALL ever reported. UKALL 14 has successfully demonstrated improved 4-year EFS and OS for ALL patients >40 years of age, and constitutes the best available evidence for RIC HCT in ALL.

The major issue of a T-depleted RIC regimen is relapse. In the context of UKALL 14, 30.3% of all patients receiving RIC allogeneic HCT were MRD positive prior to transplant, with MRD persistence following induction chemotherapy being significantly associated with an increased relapse risk (HR 2.41 (1.29–4.48) $p=0.0055$). The ALL-RIC trial attempts to address this issue by

offering radiotherapy-containing RIC conditioning in the form of cyclophosphamide/8Gy TBI/alemtuzumab as a comparator to standard chemotherapy-only reduced intensity conditioning, as well as further exploring the role of post-transplant donor lymphocyte infusion for patients with mixed donor T-cell chimerism or persistent MRD. The UKALL 14 trial highlighted an NRM with FMA reduced intensity conditioning of 20%. The ALL-RIC study will evaluate the safety of low dose TBI in an older adult allogeneic HCT population, with the hope of this being tolerable and NRM not increased. This is the first prospective, randomised study that has compared two different approaches to reduced-intensity conditioning in adult patients with ALL allograft.

ALL is a rare disease in adults and requires complex prolonged therapy. Institutions may have complex referral pathways when initial ALL therapy is delivered in a non-transplant centre and identification of suitable patients, referral to transplant centres and liaison with clinical oncologists will be a challenge even though the study is simple conceptually. In addition to these predictable logistical challenges, the impact of the COVID-19 pandemic, which has occupied 2 years of the active ALL-RIC study recruitment period to date cannot be underestimated. Research personnel have been diverted into COVID specific studies, and in conjunction with HCP exhaustion has had a profound impact on recruitment to this and other haemato-oncology studies.

Ethics and dissemination

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, and stated in the respective participating countries laws governing human research, and Good Clinical Practice. The initial protocol was approved by the East Midlands—Leicester Central Research Ethics Committee (REC Ref: 18/EM/0112) on 12 June 2018 with subsequent amendments approved on 23 July 2018 (confirmation that intrathecal methotrexate to be administered for both the control and experimental arm), 01 February 2019 (Integrated Research Application System (IRAS) form amended to allow all formulations of fludarabine), 21 October 2019 (inclusion change increase in age to 40–70; HLA identical sibling or suitable matched donor, second CR; exclusion change previous exposure to radiotherapy; trial treatment change added a later taper in patients with mismatched donors is permitted for the control arm, section made clearer about the diagnostic MRD sample, change in PIS added detail about diagnostic MRD sample), 29 October 2019 (addition of wording with regards to Epstein-Barr Virus (EBV) monitoring), 08 January 2020 (reduction in the dose of alemtuzumab dose in both arms in unrelated transplants (20mg one time daily intravenously over 2 days instead of 30mg one time daily intravenously over 2 days)). The MHRA has

given its approval of all protocol versions, the current version in use is 6.0.

Results of this trial will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by the TMG and authorship will be determined by mutual agreement and according to the publication policy of IMPACT and the British Society of Blood and Marrow Transplantation.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement N/A.

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Appendix 1: Secondary Outcome Measure analysis

The secondary outcomes are as follows; OS will be evaluated using methods of Kaplan and Meier will be compared between treatment arms using log rank tests. CIR and NRM will be presented using cumulative incidence curves and fine and grey's test will be used to compare between treatment arms. Incidence of acute and chronic GvHD, occurrence and severity of VOD will be tabulated and compared between treatment arms using Chi squared tests. Fishers exact test will be used if required. Duration of hospitalisation in the first year will be presented a median with an interquartile range and compared between treatment arms using a Mann-Whitney U test. QoL will be presented over time as medians with interquartile ranges, repeated measure models will be used to compare between treatment arms. Full donor chimerism will be tabulated and compared between treatment arms using Chi squared tests. Fishers exact test will be used if required. TBI related symptomatic pulmonary toxicity will be reported as the number and percentage of patients who experience one or more event of any grade. This will be compared between treatment arms using a Chi squared tests or Fishers exact test as appropriate. Severity of toxicities will also be tabulated.

Appendix 2: IMPACT funders

Anthony Nolan

LEUKA

NHS Blood & Transplant