MyeChild 01

International Randomised Phase III Clinical Trial in Children with Acute Myeloid Leukaemia Incorporating an Embedded Dose Finding Study for Gemtuzumab Ozogamicin in Combination with Induction Chemotherapy

Chief Investigator:

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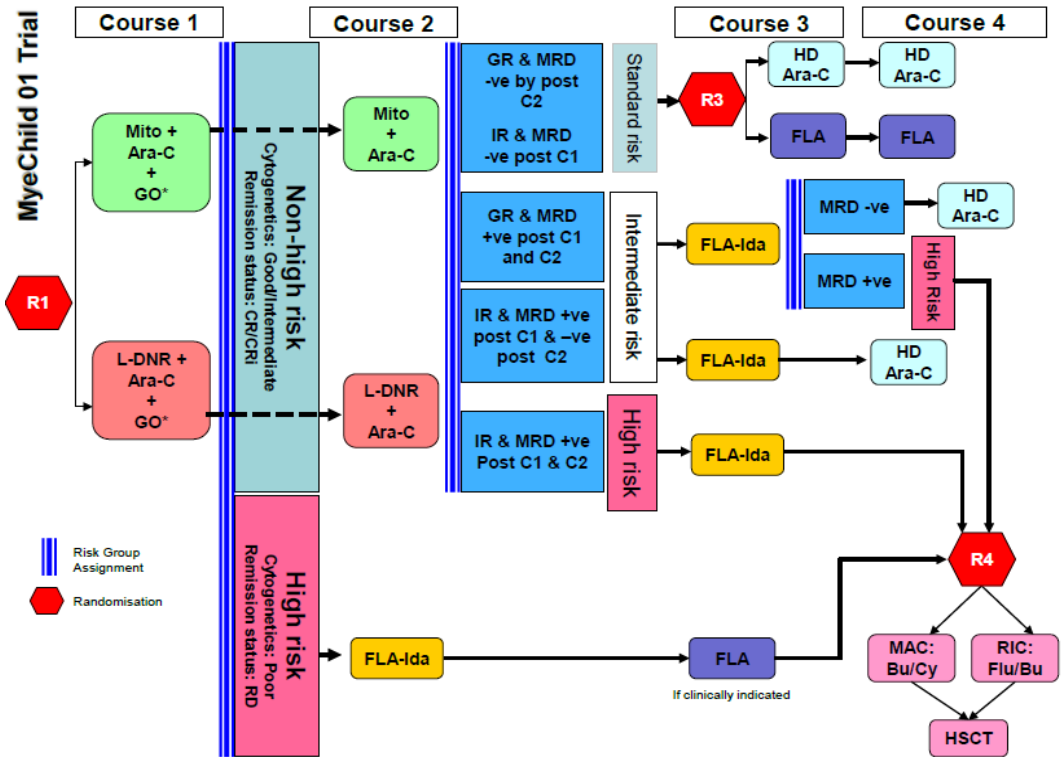
Trial Design

An international randomised phase III clinical trial incorporating an embedded dose finding study.

Trial Schema

Figure 1: Trial schema prior to opening of R2



*Patients will only receive GO with induction chemotherapy as part of the embedded gemtuzumab ozogamicin dose finding study (restricted centres), or after the first dose finding cohort has been completed and it has been shown that one dose of GO is safe when given in combination with induction chemotherapy (all centres).

Ara-C: Cytarabine

Bu/Cy: Busulfan & cyclophosphamide

CR: Complete remission

CRi: Complete remission with incomplete blood count recovery

FLA: Fludarabine & cytarabine

FLA-Ida: Fludarabine, cytarabine & idarubicin

Flu/Bu: Fludarabine & busulfan

GO: Gemtuzumab ozogamicin

GR: Good risk cytogenetics/molecular genetics

HD-Ara-C: High dose cytarabine

HSCT: Haemopoietic stem cell transplant

IR: Intermediate risk cytogenetics

L-DNR: Liposomal daunorubicin

MAC: Myeloablative conditioning

Mito: Mitoxantrone

MRD: Minimal residual disease

R1: Randomisation 1: Induction randomisation

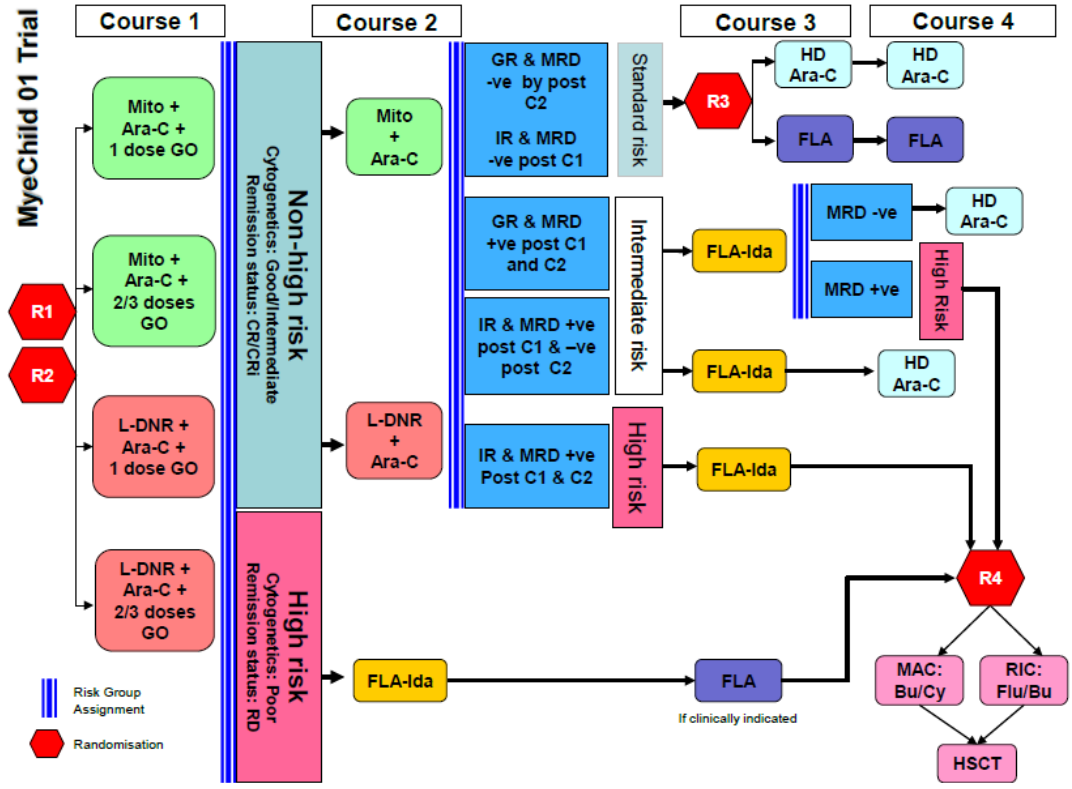
R3: Randomisation 3: Consolidation randomisation

R4: Randomisation 4: Haemopoietic stem cell transplant conditioning randomisation

RIC: Reduced intensity conditioning

RD: Resistant disease

Figure 2: Trial schema following opening of R2



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R1: Randomisation 1: Induction randomisation

R2: Randomisation 2: Gemtuzumab ozogamicin randomisation

R3: Randomisation 3: Consolidation randomisation

R4: Randomisation 4: Haemopoietic stem cell transplant conditioning randomisation

RIC: Reduced intensity conditioning

RD: Resistant disease

Primary Objectives

In newly diagnosed acute myeloid leukaemia (AML) and high risk myelodysplastic syndrome (MDS) (>10% blasts in the bone marrow):

Non-randomised

To establish the optimum tolerated number of 3 mg/m^2 doses of gemtuzumab ozogamicin (up to a maximum of 3 doses) that can be delivered safely in combination with cytarabine plus mitoxantrone or liposomal daunorubicin in induction

Randomised

1. To compare mitoxantrone (anthracenedione) & cytarabine with liposomal daunorubicin (anthracycline) & cytarabine as induction therapy.

2. To compare a single dose of gemtuzumab ozogamicin 3 mg/m^2 with the optimum tolerated number of doses of gemtuzumab ozogamicin (identified by the dose-finding study) when combined with induction chemotherapy.
3. To compare two consolidation regimens: high dose cytarabine (HD Ara-C) and fludarabine & cytarabine (FLA) in standard risk patients.
4. To compare the toxicity and efficacy of two haemopoietic stem cell transplant (HSCT) conditioning regimens of different intensity: conventional myeloablative conditioning (MAC) with busulfan/cyclophosphamide and reduced intensity conditioning (RIC) with fludarabine/busulfan.

Secondary Objectives

1. To compare the predictive value of flow and molecular MRD monitoring for relapse risk.
2. To evaluate a number of prognostic factors with a view to defining a Risk Score for children and adolescents with AML

Outcome Measures

Primary Outcome Measures

Dose finding study:	The incidence of dose limiting toxicities (DLTs)
Randomisation 1:	Event-free survival (EFS)
Randomisation 2:	EFS
Randomisation 3:	Relapse free survival (RFS)
Randomisation 4:	Early treatment related adverse reactions and RFS

Secondary outcome measures

Gemtuzumab Ozogamicin Dose Finding Study

- The nature, incidence and severity of AEs.
- Response measured by bone marrow morphology and MRD assessment
- Serum Pharmacokinetic (PK) parameters of gemtuzumab ozogamicin including clearance (CL) and volume of distribution (Vd)

All randomisations

- Complete Remission (CR) (R1 and R2 only)
- Reasons for failure to achieve CR (R1 and R2 only)
- Cumulative incidence of relapse (CIR)
- Death in CR (DCR)
- EFS
- Overall Survival (OS)
- Incidence of toxicities
- Incidence of cardiotoxicity (R1, R2 and R4 only)
- Incidence of bilirubin of grade 3 or higher (R2 and R4 only)
- Incidence of veno-occlusive disease (R2 and R4 only)
- MRD clearance after course 1 and course 2 and MRD negativity post-therapy (R1 and R2 only)
- Time to haematological recovery
- Days in hospital after each course of treatment
- Incidence of mixed chimerism at day 100 post-transplant (R4 only)
- Treatment Related Mortality (TRM) (R4 only)
- Gonadal function at 1 year post-transplant and end of study follow up (R4 only)

Patient Population

Children and young adults up to their 18th birthday with newly diagnosed AML, high risk MDS or isolated myeloid sarcoma (MS).

Sample Size

The target recruitment for the trial is up to 700 patients.

Main Inclusion and Exclusion Criteria

Inclusion Criteria:

- Newly diagnosed AML, high risk MDS (greater than 10% blasts in the bone marrow), or isolated MS (either de novo or secondary)
- Age <18 years
- No prior chemotherapy or biological therapy for AML other than that permitted in the protocol
- Normal cardiac function: fractional shortening ≥ 28%, or ejection fraction ≥ 55%
- Fit for protocol chemotherapy
- Written informed consent

Exclusion criteria:

- Acute promyelocytic leukaemia (APL)
- Myeloid leukaemia of Down Syndrome (ML DS)
- Blast crisis of chronic myeloid leukaemia (CML)

Trial Duration

The trial will recruit for approximately 5-6 years, and all patients will be followed up for a minimum of 1 year.

Treatment summary

R1: Patients will be randomised to one of two induction regimens:

- Mitoxantrone & cytarabine
- Liposomal daunorubicin & cytarabine

Gemtuzumab ozogamicin dose finding study: Patients will be allocated to receive either 1, 2 or 3 x 3mg/m^2 gemtuzumab ozogamicin.

R2: To open once cohort 2 of the dose finding study has been reviewed by the Data Monitoring Committee (DMC). Initially, patients will be randomised to receive either 1 x 3mg/m^2 or 2 x 3mg/m^2 gemtuzumab ozogamicin. If the dose finding study identifies 3 x 3mg/m^2 as the optimum tolerated number of doses then the randomisation will be amended to compare 1 x 3mg/m^2 with 3 x 3mg/m^2.

R3: Patients will be randomised to one if the two consolidation regimens (standard risk patients only):

- High dose cytarabine (HD Ara-C)
- Fludarabine & cytarabine (FLA)

R4: Patients will be randomised to one of the two HSCT conditioning regimens (high risk patients only):

- MAC: busulfan/cyclophosphamide
- RIC: busulfan/fludarabine

Trial Office Contact Details

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