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Optimising therapy in FLT3-mutated acute myeloid leukaemia

Submission date
04/07/2024

Recruitment status
Recruiting

Registration date
30/07/2024

Overall study status
Ongoing

Last Edited
16/05/2025

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
Acute myeloid leukaemia is an aggressive blood cancer and is the most common form of acute leukaemia in adults, the majority of who will die from the disease. Younger and fitter patients can have treatment aiming to cure the disease with cycles of intensive chemotherapy followed for some patients by stem cell transplant. Survival rates have gradually increased following improvements to chemotherapy, transplantation, better general care measures and new targeted drugs for patients in specific AML sub-groups. This study focuses on a subgroup of AML with mutations in the FLT3 gene, found in about one-third of AML patients. These patients have worse overall outcomes due to increased rates of early disease relapse. Clinical trials have recently identified several promising strategies to improve outcomes for patients with FLT3 AML but these approaches have not yet been combined in a single trial. Currently the standard treatment is standard intensity DA chemotherapy combined with midostaurin. We will compare this standard treatment with two new combinations. One is standard-intensity chemotherapy combined with both midostaurin and GO; this combination has already undergone pilot testing in the AML19 study and was safe and appeared very effective. The second new combination is intensified chemotherapy (FLAG-Ida) combined with midostaurin and GO. Pilot safety testing of this combination is built into this study.

Who can participate?
Patients aged 16 years and over with AML

What does the study involve?
Participants will be randomly allocated to one of the three treatment schedules. They will receive up to four cycles of intensive chemotherapy treatment, including stem cell transplant in selected cases; during this time the response of the leukaemia to treatment will be measured by blood and bone marrow tests to see whether patient outcomes are improved in terms of increased survival, reduction in rates of relapse and reduction in the need for stem cell transplant and the researchers will monitor for any increased side effects associated with the intensified treatment schedules.

What are the possible benefits and risks of participating?
Because you might get randomised to the “standard care” arm, and because we don’t yet know

whether the “test arms” are any better, there is no certainty that you will benefit directly from taking part in the trial, however, this is possible. The information from the trial results will help to improve the treatments for future patients with FLT3-mutated AML.
AML chemotherapy causes side effects and carries a risk of infection or bleeding because it damages normal blood cells as well as leukaemia cells. The usual effects of chemotherapy include hair loss, sore mouth, some nausea and sometimes vomiting although these are usually controlled with medication, damage to the immune system and problems with fertility. After each course of chemotherapy patients will be reviewed regularly by medical teams and all side effects are reported to the trial.
Midostaurin is a licenced treatment when given with DA chemotherapy, but in the “test arms” it is being used with different or additional chemotherapy drugs. The team will monitor data from the trial very closely to minimise any risk to participants. Common side effects of Midostaurin include nausea and stomach upset.
Mylotarg is licenced to treat AML in combination with DA chemotherapy. Chemotherapy will cause hair loss, sore mouth and, suppress the immune system but Mylotarg does not seem to make this worse. Liver function is a concern for patients receiving Mylotarg, therefore liver function-based eligibility criteria apply at the point of study entry and liver function test-based stipulations are applied as go/no-go before each Mylotarg dose.
FLAG-Ida (Fludarabine, Ara-C, G-CSF & Idarubicin) is a combination of three chemotherapy drugs and one “growth factor” (G-CSF) that has been used to treat AML for many years. It is more intensive than standard DA chemotherapy and may be associated with longer suppression of bone marrow following each cycle.
The combinations of drugs in experimental arms may have potential side effects and there may be risks involved in combining treatments in the experimental arms that have not yet been tested, therefore, the trial team will monitor data from the trial very closely to minimise any risk to participants. Some patients may need to delay doses of chemotherapy to allow the side effects to get better.
Experimental arm 2: Most of the possible side effects listed in the PIS are mild to moderate. However, some side effects can be very serious and life-threatening and may even result in death. It is possible that the patient's cancer may not improve during the study or may even worsen. Some side effects do not need treatment, while others generally get better with treatment. Safety data will be collected for experimental arm 2 and will be reviewed. The PIS details the full side effects of treatments and assures the patients that their doctor will be able to explain more details about the chemotherapy that they will receive and how it will be given.
The later part of AML19 included a 77-patient single-arm pilot of the combination DA-GO-Mido (termed ‘Midotarg’) to investigate the safety and preliminary efficacy of combining intensive chemotherapy with both midostaurin and GO. The combination was well tolerated, with no 60-day mortality, no excess toxicity and an encouraging overall response rate.
Experimental arm 3: Most of the possible side effects listed in the PIS are mild to moderate. However, some side effects can be very serious and life-threatening and may even result in death. It is possible that the patient's cancer may not improve during the study or may even worsen. There may be risks involved in taking the new combination of these drugs that have not yet been discovered. There is always a risk involved in taking an experimental drug, but every precaution will be taken, and patients will be closely looked after by the doctors and research nurses. If a patient suffers any side effects or injuries, or their condition gets worse, they are advised to tell their doctor/nurse immediately so that they can receive appropriate care.
The FLAG-Ida-GO-Mido schedule has not yet been piloted, therefore this arm includes a safety run-in phase where the first 20 patients will undergo enhanced pharmacovigilance. Safety data will be collected on a weekly basis following the commencement of FLAG-Ida-GO-Midostaurin. The IDMC will review safety data after 10 and 20 patients have been treated. They will particularly focus on increased haematological toxicity (delayed count recovery following courses 1 and 2), infective complications and evidence of increased 60-day mortality.

If these or other concerning toxicities are observed, the study team will act in close liaison with the IDMC. Contingencies to modify the arm 3 treatment schedule will depend on when toxicity is observed (post course 1 vs course 2) and whether it is age group-related (younger vs older patients)
Risks associated with general trial procedures:
Blood samples: Taking blood may result in pain, irritation, bruising, bleeding, and irritation at the injection site. There is also a possibility of fainting or infection
Bone marrow samples: There is a risk of pain, bleeding, problems with wound healing, bruising and/or infection
Completing QoL questionnaires: May be considered upsetting by the participants but will be completed with support from staff

Where is the study run from?
Centre for Trials Research, Cardiff (UK)

When is the study starting and how long is it expected to run for?
July 2024 to December 2030

Who is funding the study?
Cancer Research UK

Who is the main contact?
OPTIMISE-FLT3@cardiff.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-the-best-treatment-for-acute-myeloid-leukaemia-optimise-flt3

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1008479

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
SPON 1977-24, IRAS 1008479

Study information

Scientific Title
OPTIMISE-FLT3 - optimising therapy in FLT3-mutated acute myeloid leukaemia

Acronym
OPTIMISE-FLT3

Study objectives
In patients with newly diagnosed FLT3-mutated acute myeloid leukaemia (AML), does either DA-GO-Mido or FLAG-Ida-GO-Mido improve event-free survival compared to the current standard of care, DA-Mido?

Optimise-FLT3 is a Phase II/III randomised controlled trial that seeks to define the optimal combination of intensive chemotherapy with targeted agents in the treatment of patients with newly diagnosed FLT3-mutated AML, building on the results of the preceding NCRI AML19 study. The three-arm, two-stage, controlled trial compares two experimental regimens, DA-GO-Mido and FLAG-Ida-GO-Mido, against the current standard of care, DA-Mido. The study incorporates an initial pilot phase for FLAG-Ida-GO-Mido with a safety review by an independent data monitoring committee (IDMC) after 10 and 20 patients have been treated. The study population is adults with newly diagnosed FLT3mut AML who are considered suitable for intensive therapy with curative intent.

Ethics approval required
Ethics approval required

Ethics approval(s)

approved 22/08/2024, Seasonal REC (2 Redman Place, Stratford , London, E20 1JQ, United Kingdom; +44 (0)207 1048098; seasonal.rec@hra.nhs.uk), ref: 24/LO/0557

Study design
Open randomized controlled trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Acute myeloid leukemia

Interventions
Study arm 1: DA + Midostaurin
Therapy will consist of:
Course 1: DA60 3+10 + Midostaurin.
Daunorubicin IV 60 mg/m2 D1, 3, 5. Cytarabine IV 100 mg/m2 twice daily D1-10
Midostaurin PO 50 mg twice daily, D11-24
Course 2: DA50 3+8 + Midostaurin.
Daunorubicin IV 50 mg/m2 D1, 3, 5. Cytarabine IV 100 mg/m2 twice daily D1-8
Midostaurin PO 50 mg twice daily, D9-22
Courses 3-4: Cytarabine IV 3 g/m2 twice daily D1, 3, 5 (1.5 g/m2 in patients 60-69 years, 1 g/m2 daily in patients aged ≥70 years)
Midostaurin PO 50 mg twice daily, D6-19

Study arm 2: DA + GO + Midostaurin
Therapy will consist of:
Course 1: DA60 3+10 + GO + Midostaurin.
Daunorubicin IV 60 mg/m2 D1, 3, 5. Cytarabine IV 100 mg/m2 twice daily D1-10
Gemtuzumab Ozogamicin (GO) IV 3 mg/m2 (capped at 5 mg) D1 + 4, delayed to D4 + 7 if WBC ≥30 x 10e9/L
Midostaurin PO 50 mg twice daily, D11-24
Course 2: DA50 3+8 + Midostaurin.
Daunorubicin IV 50 mg/m2 D1, 3, 5. Cytarabine IV 100 mg/m2 twice daily D1-8
Midostaurin PO 50 mg twice daily, D9-22
Courses 3-4: Cytarabine IV 3 g/m2 twice daily D1, 3, 5 (1.5 g/m2 in patients 60-69 years, 1 g/m2 daily in patients aged ≥70 years)
Midostaurin PO 50 mg twice daily, D6-19

Study arm 3: FLAG-Ida + GO + Midostaurin
Therapy will consist of:
Course 1: FLAG-Ida + GO + Midostaurin
Fludarabine IV 30 mg/m2 D2-6. Cytarabine IV 2 g/m2 D2-6 (1 mg/m2 in patients ≥60 years)
G-CSF S/C 263 µg (or equivalent 300 µg) D1-7. Idarubicin IV 8 mg/m2 D4-6. GO IV 3 mg/m2 D2 (capped at 5 mg/m2 and delayed to D5 if WBC ≥30 x 10e9/l). Midostaurin PO 50 mg twice daily, D7-20.
Course 2: FLAG-Ida + Midostaurin

Fludarabine IV 30mg/m2 D2-6. Cytarabine IV 2 g/m2 D2-6 (1 g/m2 in patients ≥60 years)
G-CSF S/C 263 µg (or equivalent 300 µg) D1-7. Idarubicin IV 8 mg/m2 D4-5. Midostaurin PO 50 mg twice daily, D7-20.
Course 3-4: Cytarabine IV 3 g/m2 twice daily D1, 3, 5 (1.5 g/m2 in patients 60-69 years, 1 g/m2 daily in patients aged ≥70 years)
Midostaurin PO 50 mg twice daily, D6-19

Maintenance
On completion of chemotherapy, all patients who are not proceeding to allogeneic stem cell transplant in first remission will receive maintenance Midostaurin PO 50 mg twice daily, for 12 x 28-day cycles.

The trial is a randomised Phase II/III trial. Randomisation will be performed using a computer-implemented minimisation algorithm by the CTR.
At trial entry patients will be randomised (1:1:1) between the three treatment arms, balancing randomisation by FLT3 mutation type, NPM1 status and age, and this information must be available at the point of randomisation (unless the patient is entering as a medical emergency using PIS/ICF2, in which case FLT3 and/or NPM1 mutation may be recorded as to be confirmed).

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Gemtuzumab ozogamicin, midostaurin, daunorubicin, cytarabine, fludara, idarubicin, filgrastim

Primary outcome(s)
Event-free survival (EFS) time, measured in days from the date of randomisation until the date of the first of any EFS events below. Patients still alive and event-free at the end of follow-up will be censored at the date of the most recent documented blood or bone marrow test that shows parameters consistent with ongoing disease response. Event data will be collected for the duration of follow-up until 2 years after the last patient has completed protocol treatment.

Specified EFS events will include:
1. Death from any cause
2. Failure to achieve complete remission (CR), CR with partial hematologic recovery (CRh) or CR with incomplete count recovery (CRi) after two chemotherapy cycles
3. MRD relapse, as defined by the European Leukaemia Network
Morphological and MRD remission status will be assessed by bone marrow aspiration following each cycle of chemotherapy in the context of recovery of peripheral blood count. MRD remission status is assessed by NPM1 qPCR (NPM1 co-mutated patients) and by flow cytometry in non-NPM1 co-mutated patients.

Key secondary outcome(s))
1. Incidence of complete remission (CR, CRh and CRi by ELN2022) within two cycles: morphological remission status assessed by repeat bone marrow aspiration following each cycle of chemotherapy in the context of recovery of peripheral blood count
2. Number of deaths within 30 and 60 days from randomisation
3. Overall survival time, measured in days from the date of randomisation until the date of death

from any cause. Patients still alive at the end of follow-up will be censored at the date last seen in clinic (telephone confirmation will be acceptable).
4. Time to haematological relapse, measured from the date of documentation of 1st CR, CRi or CRh until the date of frank relapse. Patients who have not relapsed at the end of follow-up will be censored at the date of last documented blood or bone marrow test that shows parameters consistent with ongoing disease response.
5. The number and percentage of patients with MRD negativity after cycle 2 by RT-qPCR (for NPM1mut) or flow cytometry
6. Time to MRD relapse for patients with a monitored MRD marker, measured from the date of first molecular complete remission, until the date of MRD relapse (as defined by the ELN2022 23). Patients who are MRD negative will be censored at the date of last MRD assessment.
7. Cumulative incidence of grade 3 and 4 toxicity (by CTCAE version 5) over the duration of follow-up. The worst grade of toxicity will be reported.
8. Cumulative resource use including duration of hospital admissions, blood product usage (red cells, platelets) and days on intravenous antibiotics and antifungals. These measures will be collected following each cycle of intensive chemotherapy and compared by individual chemotherapy cycle and cumulatively by study arm
9. Rates of allogeneic stem cell transplant by study arm: in first remission and at later timepoints
10. Health-related quality of life assessed during treatment and over 2 years of post-treatment follow-up. Measured by EORTC QLQ-C30 and EQ-5D-5L following treatment courses 2 and 4 then 6, 12 and 24 months from the end of treatment

Completion date
31/12/2030

Eligibility

Key inclusion criteria
1. Diagnosis of AML
2. Age ≥16 years (no specified upper age limit)
3. Considered fit for intensive AML therapy by the treating physician
4. Confirmed FLT3 ITD or TKD mutation (or FLT3 status unknown but requires urgent therapy - see below*)
5. Serum creatinine less than or equal to 1.5 x ULN (upper limit of normal)
6. Serum Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) less than or equal to 2.5 x ULN and bilirubin less than or equal to 2 x ULN
7. A negative pregnancy test within 2 weeks prior to trial entry in WOCBP (to be repeated throughout the trial prior to each course of protocol treatment)
8. Sexually mature males and females must agree to use an adequate and medically accepted method of contraception throughout the study and for 6 months following treatment if they or their sexual partners are women of childbearing potential (WOCBP)
9. WHO performance status 0-2
10. Written informed consent

*FLT3-mutated AML is associated with proliferative disease features such as hyperleukocytosis (high white blood cell count) and may present as a medical emergency. It is important that the full clinical spectrum of FLT3-mutated AML is represented in Optimise-FLT3, including hyper-proliferative cases. Should the treating physician feel that the safety of an individual patient could be compromised by delaying therapy while awaiting FLT3 genotyping, they may, on discussion with the study team, proceed with study entry (using PIS2), randomisation and treatment provided all other eligibility criteria are met. Any patients who enter the trial and are

subsequently found to have wild-type FLT3 will be considered evaluable for safety/toxicity analysis but will be replaced with additional FLT3-mutated cases to maintain statistical power for the clinical efficacy endpoints and equipoise between arms.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 years

Sex
All

Key exclusion criteria
1. Receipt of any previous therapy for AML or any antecedent haematological condition (the use of oral hydroxycarbamide to control white blood cell count is permitted)
2. Other active malignancy requiring treatment
3. Patients who are pregnant or lactating
4. Uncontrolled infection with Human Immunodeficiency Virus (HIV) or Hepatitis B or C. Patients with known chronic infections who are receiving or have completed therapy and have recent documented negative viral PCR tests are not excluded
5. Blast transformation of chronic myeloid leukaemia (CML)

Date of first enrolment
01/02/2025

Date of final enrolment
31/01/2031

Locations

Countries of recruitment
United Kingdom

Denmark

New Zealand

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
Cardiff University

ROR
https://ror.org/03kk7td41

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Requests for data would need to be formally made to Cardiff University as Sponsor and only after the main publication and final report is published.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other files	Flowchart	31/05/2024	18/07/2024	No	No
Protocol file	version 1.1	12/08/2024	16/09/2024	No	No