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Attenuated dose rituximab with chemotherapy in chronic lymphocytic leukaemia (CLL)

Submission date	Recruitment status	[X] Prospectively registered
17/09/2008	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
25/09/2008	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
24/03/2022	Cancer	

Plain English summary of protocol
http://www.cancerhelp.org.uk/trials/a-trial-adding-rituximab-mitoxantrone-to-fludarabine-cyclophosphamide-treat-chronic-lymphocytic-leukaemia

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2009-010998-20

Protocol serial number
HTA 07/01/38; Sponsor ref: HM09/8848

Study information

Scientific Title
A randomised, phase IIB trial in previously untreated patients with chronic lymphocytic leukaemia (CLL) to compare fludarabine, cyclophosphamide and rituximab (FCR) with FC, mitoxantrone and low dose rituximab (FCM-miniR)

Acronym
ARCTIC

Study objectives
This trial aims to establish whether the addition of mitoxantrone (M) with a reduced dose of rituximab (R), to fludarabine (F) and cyclophosphamide (C) - FCM-miniR is as effective as FCR in terms of response in patients with previously untreated chronic lymphocytic leukaemia (CLL).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Leeds (East) Research Ethics Committee, 25/06/2009, ref: 09/H1306/54

Study design
Multi-centre phase II open non-inferiority randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic lymphocytic leukaemia (CLL)

Interventions
Patients will be randomised to receive 6 cycles of either FCR or FCM-miniR according to the following regimens:

Fludarabine, cyclophosphamide and rituximab (FCR):
Fludarabine (oral)* 24 mg/m^2/day, Days 1 to 5
Cyclophosphamide (oral)* 150 mg/m^2/day, Days 1 to 5
Rituximab (intravenous) 375 mg/m^2, Day 1 (Cycle 1)
Rituximab (intravenous) 500 mg/m^2, Day 1 (Cycle 2-6)
Cycles of FCR are repeated every 28 days for a total of 6 cycles.
G-CSF (lenograstim 263 mg/day) for days 7 to 13 is recommended for all subsequent cycles in patients who have to have a previous dose delay due to neutropenia.

*Patients should be questioned regarding nausea and vomiting or diarrhoea occurring with the prior cycle of therapy and if this is present then the fludarabine and cyclophosphamide should

be given via the intravenous route due to concerns over drug absorption. Intravenous fludarabine (25 mg/m^2/day for 3 days) and cyclophosphamide (250mg/m2/day for 3 days) regimens are recommended if the oral regimen is not tolerated.

Fludarabine, cyclophosphamide, rituximab and mitoxantrone (FCM-miniR):
Fludarabine (oral)* 24 mg/m^2/day, Days 1 to 5
Cyclophosphamide (oral)* 150 mg/m^2/day, Days 1 to 5
Mitoxantrone (intravenous) 6 mg/m^2/day, Day 1
Mini Rituximab (intravenous) 100 mg, Day 1
Cycles of FCM-miniR are repeated every 28 days for a total of 6 cycles.
G-CSF (lenograstim 263 mg/day) for days 7 to 13 is recommended for all subsequent cycles in patients who have to have a previous dose delay due to neutropenia.

*Patients should be questioned regarding nausea and vomiting or diarrhoea occurring with the prior cycle of therapy and if this is present then the fludarabine and cyclophosphamide should be given via the intravenous route due to concerns over drug absorption. Intravenous fludarabine (25 mg/m^2/day for 3 days) and cyclophosphamide (250 mg/m^2/day for 3 days) regimens are recommended if the oral regimen is not tolerated.

Patients will be evaluated every 6 months after the end of therapy until disease progression requiring therapy or until 2 years post-randomisation. All patients will be followed-up for survival until death as part of a long term follow-up registry which is currently in set-up.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Mitoxantrone, rituximab, fludarabine, cyclophosphamide

Primary outcome(s)
Proportion of patients achieving a complete response (CR), as defined by the IWCLL criteria. A formal assessment of response by IWCLL criteria will be made 3 months after the end of therapy.

Key secondary outcome(s))
1. Proportion of patients with undetectable minimal residual disease (MRD) according to the IWCLL Response Criteria, assessed at baseline and 3 months after the end of therapy. Patients who are MRD negative at the end of treatment will also be followed up every 6 months after the end of therapy until disease progression requiring therapy or 2 years post-randomisation. All patients will be followed up for survival until death.
2. Overall response rate defined as complete or partial remission by IWCLL Criteria at 3 months after the end of therapy
3. Progression-free survival at 2 years
4. Overall survival at 2 years
5. Safety and toxicity. Adverse events (AEs) related to the treatment will be collected from randomisation until 30 days after the last dose of treatment with FCR or FCM-miniR.
6. Economic evaluation (time frame not yet finalised)

Completion date

31/12/2011

Eligibility

Key inclusion criteria
1. Both males and females, at least 18 years old
2. B-CLL with a characteristic immunophenotype
3. Binet's Stages B, C or Progressive Stage A
4. Requiring therapy by the International Workshop on CLL (IWCLL) criteria in that they must have at least one of the following: Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia
5. Massive (i.e. 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
6. Massive nodes (i.e. 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
7. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months as long as the lymphocyte count is over 30 x 10^9/L
8. A minimum of any one of the following disease-related symptoms must be present:
8.1. Unintentional weight loss more than or equal to 10% within the previous 6 months
8.2. Significant fatigue (i.e. Eastern Cooperative Oncology Group PS 2 or worse; cannot work or unable to perform usual activities)
8.3. Fevers of greater than 38.0°C for 2 or more weeks without other evidence of infection
8.4. Night sweats for more than 1 month without evidence of infection
9. No prior therapy for CLL
10. World Health Organization (WHO) performance status (PS) of 0, 1 or 2
11. Able to provide written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Prior therapy for CLL
2. Active infection
3. Past history of anaphylaxis following exposure to rat or mouse derived CDR-grafted humanised monoclonal antibodies
4. Pregnancy, lactation or women of child-bearing potential unwilling to use medically approved contraception whilst receiving treatment
5. Men whose partners are capable of having children but who are not willing to use appropriate medically approved contraception during the study, unless they are surgically sterile

6. Central nervous system (CNS) involvement with CLL
7. Mantle cell lymphoma
8. Other severe, concurrent diseases or mental disorders
9. Known HIV positive
10. Patient has active or prior hepatitis B or C
11. Active secondary malignancy excluding basal cell carcinoma
12. Persisting severe pancytopenia (neutrophils <0.5 x 10^9/l or platelets <50 x 10^9/l) or transfusion dependent anaemia unless due to direct marrow infiltration by CLL
13. Active haemolysis (patients with haemolysis controlled with prednisolone at a dose 10 mg or less per day can be entered into the trial)
14. Patients with a creatinine clearance of less than 30 ml/min (either measured or derived by the Cockcroft formula)

Date of first enrolment
01/01/2009

Date of final enrolment
31/12/2011

Locations

Countries of recruitment
United Kingdom

England

Ireland

Study participating centre
St James's University Hospital
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Sponsor information

Organisation
Leeds Teaching Hospitals NHS Trust (UK)

ROR
https://ror.org/00v4dac24

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2017		Yes	No
Results article	results	01/11/2017		Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Plain English results			24/03/2022	No	Yes