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A study using a response-based combination therapy of rituximab and ibrutinib in patients with post-transplant lymphoproliferative disorder (PTLD)

Submission date
21/11/2016

Recruitment status
No longer recruiting

Registration date
22/11/2016

Overall study status
Completed

Last Edited
09/07/2025

Condition category
Haematological Disorders

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
After an organ or bone marrow transplant, patients with weakened immune systems can develop a condition called post-transplant lymphoproliferative disorder (PTLD). This occurs when a group of white blood cells called 'B cells' grow out of control. The standard of treatment for PTLD in the UK is the initial use of the 'monoclonal antibody' drug rituximab, which is the standard of care for other types of lymphoma and can be successful in treating PTLD. However, the majority of patients may not respond very well to rituximab on its own and, in these cases, chemotherapy will be added to rituximab to achieve or improve a response. This involves having a course of rituximab (R), together with a course of a combination of other drugs called cyclophosphamide, vincristine, doxorubicin and prednisolone (CHOP). Studies have shown that R-CHOP is effective at treating PTLD but patients are at a higher risk of infection and this treatment has a higher risk of causing damage to the transplanted organ and hence patients are likely to experience additional side effects. A drug called ibrutinib has recently been licensed for use in other haematological conditions. Studies of ibrutinib alone or ibrutinib combined with rituximab or R-CHOP have shown these treatments to be effective at treating other forms of lymphoma. The aim of this study is to find out if adding ibrutinib to rituximab (IR) can improve the initial response to rituximab and if it could result in fewer patients needing to have R-CHOP treatment.

Who can participate?
Adults with PTLD

What does the study involve?
There are two stages of treatment involved in this trial. During the first stage, patients receive ibrutinib and rituximab for up to seven weeks. Ibrutinib treatment is given as an oral capsule. This treatment starts on day one and will be taken once a day, every day. Rituximab is given through a drip (infusion) once a week for the first four weeks of treatment. During week seven, response to the treatment is assessed using a CT scan. Patients who have responded well to the

first stage of treatment continue to take ibrutinib for a further 12 weeks and receive a further four doses of rituximab (every three weeks). Patients who have not responded to the initial stage of treatment or the response is not adequate, continue to receive ibrutinib and rituximab in the same pattern. Further to this they also receive four other drugs – CHOP chemotherapy (doxorubicin, vincristine, cyclophosphamide and prednisolone). Doxorubicin, vincristine and cyclophosphamide are given on the same day as rituximab and they will be given as an infusion. Prednisolone tablets are taken over five days starting from the day of the infusions. These infusions also take place once every three weeks. If at any time during the first stage of treatment the PTLD becomes worse, the patient starts IR-CHOP therapy immediately. It is expected that treatment will last for approximately 5 months. At the end of the study period, patients will stop taking medication. Patients are followed up every three months for two years.

What are the possible benefits and risks of participating?
There is no guaranteed benefit to taking part in this study. It is possible that the disease may respond to the study treatment and the patient will be able to continue taking the ibrutinib for up to 5 months. The information gained from this study may help improve treatment for other people with PTLD in the future. As with any drugs, ibrutinib, rituximab and CHOP can cause unwanted effects, these will be explained to the patient by the study doctor. Some of the assessments the patient will receive may pose small risks which will be explained by the study doctor; bone marrow biopsy, blood sampling, CT/PET and MUGA scans. These assessments would also be received as part of normal care.

Where is the study run from?
Queen Elizabeth Hospital and up to 20 hospitals from across the UK (UK)

When is the study starting and how long is it expected to run for?
January 2015 to September 2022

Who is funding the study?
Bloodwise (UK)

Who is the main contact?
TIDAL@trials.bham.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-ibrutinib-and-rituximab-for-post-transplant-lymphoproliferative-disorder-tidal

Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2015-005454-35

Protocol serial number
32663

Study information

Scientific Title
Risk-stratified sequential Treatment with Ibrutinib and Rituximab (IR) and IR-CHOP for De-novo post-transplant Lymphoproliferative disorder (PTLD)

Acronym
TIDaL

Study objectives
The aim of this study is to find out if adding ibrutinib to rituximab (IR) can improve the initial response to rituximab and result in fewer patients requiring R-CHOP treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North East – Tyne & Wear South Research Ethics Committee, 15/09/2016, ref: 16/NE/0279

Study design
Non-randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Specialty: Haematology, Primary sub-specialty: Haematology; UKCRC code/ Disease: Blood/ Other diseases of blood and blood-forming organs

Interventions
All patients registered to the trial will commence ibrutinib (oral capsules taken daily) and rituximab (weekly infusion for 4 weeks) therapy. After an initial 7 week treatment period the response to therapy will be assessed via CT scan. Patients who have responded well to treatment will continue to receive ibrutinib daily (up to day 133) with a further 4 rituximab infusions at 3 weekly intervals. Patients who have not responded will also continue to receive

ibrutinib and rituximab, with the addition of CHOP chemotherapy at 3 weekly intervals. The treatment will last for up to 5 months in total and patients will be followed up for 2 years (visits to occur every 3 months).

Intervention Type
Other

Primary outcome(s)
Complete remission rate is measured using CT scanning after 7 weeks of therapy.

Key secondary outcome(s))
1. Event free survival (events defined as treatment discontinuation due to toxicity, disease progression and death) is measured by medical record review at patient visits during treatment and follow up visits
2. Response (complete remission (CR) partial response (PR), stable disease (SD) and progressive disease (PD)) is evaluated by CT and PET scans after 7 weeks of therapy and at the end of treatment
3. Overall survival by medical record review at follow up time points
4. Progression free survival is measured by CT scan at 12 months and medical record review at follow up visits
4. Treatment-related mortality is measured by medical record review at time of patient death
5. Tolerability (defined in terms of absence of toxicities related to ibrutinib quantified by the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) (version 4)) is measured by clinical observations and medical record review at patient visits throughout the duration of treatment
6. Dose interruptions, dose reductions or discontinuations is measured by medical record review at patient visits throughout the duration of treatment
7. Grade III and IV leucocytopenia and grade III and IV infections by treatment group is measured by blood tests and clinical observations at patient visits throughout the duration of treatment
8. Entry into low risk arm after IR therapy is measured by response to treatment (CT scan) at seven weeks of therapy

Completion date
16/09/2022

Eligibility

Key inclusion criteria
1. CD-20 positive PTLD with or without EBV association, confirmed after biopsy or resection of tumour
2. Measurable disease of > 2.0 cm in diameter and/or bone marrow involvement
3. Patients having undergone heart, lung, liver, kidney, pancreas, small intestine transplantation, or a combination of the above organ transplantations or PTLD post ASCT or those with meningeal and CNS involvement
4. Platelet count ≥ 100 x 109/L or ≥ 50 x 109/L if bone marrow involvement independent of transfusion support in either situation •
Absolute neutrophil count (ANC) ≥1 x 109/L, independent of growth factor support (GCSF)
5. Adequate renal and hepatic function defined as the following:
5.1. Calculated creatinine clearance ≥ 50 mL/min
5.2. AST or ALT ≤ 3.0 times the upper limit of normal (ULN) of the institution's normal range
5.3. Bilirubin ≤ 1.5 × ULN. Patients with known Gilbert's syndrome may have a bilirubin level > 1.5

× ULN*
6. Prothrombin time (PT) (or international normalised ratio (INR)) and partial thromboplastin time (PTT) not to exceed 1.2 times the ULN* (*patients with abnormal bilirubin/PT/INR/PTT due to PTLD may be included in the study)
7. Left ventricular ejection fraction (LVEF) > 50% or report stating left ventricular function is satisfactory or normal
8. ECOG performance score ≤ 2
9 Clinically insufficient response to an upfront reduction of immunosuppression with or without antiviral therapy
10. Age at least 16 years
11. Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 12 months after treatment discontinuation. For males, these restrictions apply for 12 months after the last dose of study drug.
12. Able to give written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Complete surgical extirpation of the tumour or irradiation of residual tumour masses
2. Upfront treatment with rituximab or chemotherapy within the previous 3 months
3. Severe organ dysfunction not related to PTLD
4. T-cell PTLD
5. Patients requiring concomitant use of strong CYP3A4/5 inhibitors/inducers, or who have received anticoagulation treatment with warfarin or vitamin K antagonists within one week of registration
6. Known to be HIV-positive
7. Active hepatitis B or other severe, active infection which would preclude the patient from trial therapy in the clinical judgement of the treating Investigator
8. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.
9. Life expectancy less than 6 weeks
10. Any contraindication to the IMPs according to the Summary of Product Characteristics (SmPC)

Date of first enrolment
12/12/2016

Date of final enrolment
24/03/2020

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Queen Elizabeth Hospital
Centre for Clinical Haematology
Morris House
Edgbaston
Birmingham
United Kingdom
B15 2TH

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Bloodwise

Alternative Name(s)

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
The current data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		21/04/2024	22/04/2024	Yes	No
Basic results			27/03/2025	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 8.0	09/11/2018	22/09/2022	No	No
Protocol file	version 9.0	15/12/2022	25/07/2023	No	No