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Investigating COVID-19 infection in patients with acute myeloid leukaemia (AML) undergoing chemotherapy

Submission date
20/05/2021

Recruitment status
No longer recruiting

Registration date
28/11/2022

Overall study status
Completed

Last Edited
30/07/2024

Condition category
Cancer

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The pandemic of Coronavirus disease 2019 (COVID-19) is having major implications on healthcare globally with an estimated around 1-2% of patients dying from the disease. This risk increases with age and this is particularly important for patients with cancer where age is also a risk factor. It is possible a large proportion of the population could become infected with COVID-19. As the prevalence of COVID-19 in the UK is not known due to limited testing, it is not possible to accurately estimate what proportion of patients will have a history of, or will go on to develop, COVID-19. In patients over the age of 60, the hospitalisation rate is estimated to be around 16%, with a quarter requiring Intensive care support and a death rate of 2%.

Acute Myeloid Leukaemia (AML) is a type of cancer that starts in the bone marrow, where the blood cells that fight infections in the body are produced. AML affects predominantly the elderly with a peak of cases at over 70 years of age. There is some early evidence to suggest that patients with cancer are more likely to develop severe COVID-19 disease. Patients during the pandemic will continue to develop AML and it is not possible to delay starting treatment for this aggressive disease for the number of months it may take for the current pandemic to subside. AML is potentially curable with intensive chemotherapy and therefore the recommendation has been not to delay starting treatment. However, there is no data to inform practice in patients with AML who develop COVID-19. A recommendation is to test all patients with a new diagnosis of AML for COVID-19. At present, it is not clear whether patients should be managed with intensive, inpatient standard chemotherapy schedules that will leave patients more immunosuppressed but with better cancer survival rates. This will also require a longer bed occupancy which is a critical issue during this coronavirus pandemic. Furthermore, early evidence suggests that SARS-CoV2 transmission between cancer patients is largely dependent on hospital-acquired transmission. Therefore, it will be important to understand the survival of patients treated with both intensive and non-intensive chemotherapy schedules during this era.

A further complication is that patients with AML are well established to be vulnerable to severe invasive bacterial and fungal infections; infection remains a major cause of morbidity and mortality in AML. It is important to rapidly define the impact of COVID-19 infection on the

mortality rate and how best to manage COVID-19 alongside these expected bacteria/fungal invasive infections.

This study aims to collect data on the outcomes of patients with AML who develop COVID-19 infection, and the rates and severity of all infections in patients with AML undergoing intensive chemotherapy, including in those who have recovered from prior COVID-19 infection or who develop COVID-19. This information will be essential to design new studies and update current recommendations.

Who can participate?
Adult patients with acute myeloid leukaemia (AML) or Myelodysplastic Syndrome With Excess Blasts (MDS-EB2) currently receiving, or due to receive, treatment.

What does the study involve?
Demographic data and medical history will be collected for all participants at the start of the study. This will include pre-existing conditions such as diabetes and any history of COVID-19 infection. All patients will also be tested at baseline for COVID-19 and this data will be collected. Data will also be collected on the patient's treatment plan for their AML.

For the 6 months after joining the study, data will be collected on each participant on a weekly basis. Information can be obtained from the hospital notes so patients do not need to attend the clinic. This will include data on any COVID-19 diagnosis, symptoms and outcome, and data on any hospital admissions. Type of infection, diagnostic assessments, antibiotic/antifungal prophylaxis, and how these are treated will be reported. At monthly intervals, there will be an additional form to provide data on any bone marrow assessments the patient has had for their AML and also their survival status. Patients will be followed up for survival until the end of the study. Then, for the following 6 months, patients will be followed up 3 monthly for evidence of COVID-19 infection, AML treatment, and disease response and survival.

If the patient has consented to participate in the sampling sub-study, blood, stool, saliva, and sputum samples would be requested upon entry into the sub-study, and every month for 6 months. Additional samples are requested if the patient is hospitalised with an infection (upon admission to hospital, and 4 weeks later). If a patient doesn't wish to provide a certain sample, or if it is inappropriate to ask for a sample at a certain timepoint, the time point should be missed.

What are the possible benefits and risks of participating?
Participants will be fully informed of the risks and benefits of taking part in the study, along with the burdens involved. As the main study is a non-interventional study that will only collect data and there are no assessments additional to standard of care, the risks are minimal. Any additional risks and burdens through participating in the optional sampling sub-study have been described in the PIS. It is hoped the information gained from this study may help to improve the care of AML patients in the future. The sample collection in the sub-study will not result in any additional visits for patients and blood samples would be taken at the same time as any routine samples.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
From January 2020 to March 2023

Who is funding the study?
Cure Leukaemia (UK) and the National Institute for Health Research (UK)

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

Contact information

Type(s)
Principal Investigator

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Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
282870

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 45718, IRAS 282870

Study information

Scientific Title
The impact of COVID-19 on patients with AML undergoing chemotherapy: an epidemiological study

Acronym
PACE

Study objectives
To understand the incidence of COVID-19 infection during treatment of Acute Myeloid Leukaemia (AML)

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 01/05/2020, North of Scotland Research Ethics Committee (Currently being held remotely via Zoom video-conference; +44 (0)1224558458; gram.nosres@nhs.scot), ref: 20/NS/0059

Study design
Observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Acute myeloid leukaemia, COVID-19 (SARS-CoV-2 infection)

Interventions
Patients with AML may participate in this study if they have a newly diagnosed disease, if they are currently receiving treatment for AML or if their AML has returned (relapsed) and they are due to have treatment with chemotherapy. It is thought approximately 50% of patients will be receiving intensive chemotherapy and around 50% will be receiving non-intensive chemotherapy.

Demographic data, medical history, and ECOG performance status will be collected for all patients at baseline. This will include pre-existing conditions such as diabetes and any history of COVID-19 infection. All patients will also be tested at baseline for COVID-19 as per the standard of care and this data will be collected. Data will also be collected on the patient's treatment plan for their AML.

For 6 months following study entry, data will be collected on each patient for the study on a weekly basis. Information can be obtained from the hospital notes so patients do not need to attend the clinic. This will include data on any COVID-19 diagnosis, symptoms and outcome, and data on any hospital admissions. Type of infection, diagnostic assessments, antibiotic/antifungal prophylaxis, and treatment will be reported.

At monthly intervals, there will be an additional form to provide data on any bone marrow assessments the patient has had for their AML and also their survival status. Patients will be followed up for survival until the end of the study.

For the following 6 months, patients will be followed up 3 monthly for evidence of COVID-19 infection, AML treatment, and disease response and survival.

If the patient has consented to the sampling sub-study, blood, stool, saliva, and sputum samples would be requested upon entry into the sub-study, and every month for 6 months. Additional samples are requested if the patient is hospitalised with an infection (upon admission to hospital, and 4 weeks later). If a patient doesn't wish to provide a certain sample, or if it is inappropriate to ask for a sample at a certain timepoint, the time point should be missed.

Intervention Type
Other

Primary outcome measure
Incidence of COVID-19 infection developing during AML treatment measured using SAR-CoV-2 PCR test and from hospital records from baseline until 4 weeks subsequent to the last cycle of treatment

Secondary outcome measures
Prospective study outcomes:
1. Symptoms and severity of COVID-19 infection in patients with AML measured using patient notes (of patient hospitalisation, requiring oxygen, and ITU admission), completing weekly follow-up forms (was oxygen saturation <92% and does the patient have sustained increased respiratory rate?) between baseline and 24 months
2. Survival at Day 30 and 60, with or without a diagnosis of COVID-19 at presentation, or at any stage, measured using CRFs, monthly follow up forms, treatment form, and baseline form at 30 and 60 days
3. Overall survival measured using patient notes at first diagnosis until death
4. The number of episodes of bacteraemia/presumed fungal infection in AML patients measured using patient notes, all documented in the admission/infection form (reviewing if blood culture

was performed, serum fungal test performed, and CT chest performed) between baseline and 24 months
5. The severity of episodes of bacteraemia/presumed fungal infection in AML patients measured using the length of the episode, days in ICU, duration of hypotension, and CTCAE V4 grading between baseline and 24 months
6. Use of anti-viral agents as prophylaxis and therapy in this high-risk population (including convalescent plasma) measured using the number of occasions anti-viral agents were used (including convalescent plasma), and the number and proportion of patients who have received them, recorded in hospital records between baseline and 24 months
7. Prevalence of prior COVID-19 infection at the time of AML presentation measured using the presence of positive IgG (although recognising that some patients with AML may have significant hypogammaglobulinaemia) at baseline
8. Development of COVID-19 antibodies (IgG and/or IgM) during AML treatment measured using the presence of positive IgG (although recognising that some patients with AML may have significant hypogammaglobulinaemia) at 24 months

Retrospective cohort outcomes:
1. Symptoms and severity of COVID-19 infection in patients with AML or MDS-EB2 using SAR-CoV-2 PCR test and from hospital records at the time COVID-19 infection is identified

Vaccine cohort outcomes:
1. Immune response to COVID-19 vaccination at 4 weeks following vaccination (first, second, third and fourth vaccine where possible) in patients with AML or MDS-EB2 measured using blood samples taken (antibody and t-cell response data) at 4 weeks after vaccination
2. Immune response to COVID-19 vaccination at 6 months post second vaccine (or pre-third dose) in patients with AML or MDS-EB2 measured using blood samples taken (antibody and t-cell response data) at 6 months after the second vaccination
3. Influence of treatment regimen on the immune response to COVID-19 vaccination in patients with AML or MDS-EB2 measured using vaccine treatment and vaccine form an antibody and t-cell response data from blood samples taken at all timepoints (4 weeks post 1st, 2nd, 3rd, and 4th vaccines and 6 months post 2nd vaccine)
4. Influence of disease status on the immune response to COVID-19 vaccination in patients with AML or MDS-EB2 measured using baseline form, and antibody and t-cell response data from blood samples taken at all timepoints (4 weeks post 1st, 2nd, 3rd, and 4th vaccines and 6 months post 2nd vaccine)

Overall study start date
01/05/2020

Completion date
31/03/2023

Eligibility

Key inclusion criteria
1. Acute myeloid leukaemia (AML) including known AML presenting with relapse or Myelodysplastic Syndrome With Excess Blasts (MDS-EB2)
2. Currently receiving (at any treatment stage), or planned for, intensive (i.e. curative intent) or non-intensive chemotherapy. Intensive treatment includes regimens including Daunorubicin /Cytarabine, Fludarabine/Cytarabine/Idarubicin, intermediate/high dose Cytarabine, CPX-351, Gemtuzumab Ozogamacin, Midostaurin. Non-intensive treatments include Azacitidine, low dose

Cytarabine, and Venetoclax based regimens.
3. Written informed consent to participate

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 200; UK Sample Size: 200

Total final enrolment
321

Key exclusion criteria
1. Aged <16 years
2. Undergoing allogeneic stem cell transplant at trial entry
3. Supportive care only (including hydroxycarbamide alone)
4. Acute promyelocytic leukaemia (APML)

Date of first enrolment
13/05/2020

Date of final enrolment
30/06/2021

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
Oxford

United Kingdom
OX3 9DU

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
St Thomas' Hospital
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Study participating centre
Guy's and St Thomas' NHS Foundation Trust
St Thomas' Hospital
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Study participating centre
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BT9 7AB

Study participating centre
Cardiff and Vale NHS Trust
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Heath Park

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CF14 4XW

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
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NW1 2PG

Study participating centre
The Royal Wolverhampton NHS Trust
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WV10 0QP

Study participating centre
James Paget University Hospitals NHS Foundation Trust
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Study participating centre
University Hospitals Coventry and Warwickshire NHS Trust
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Study participating centre
University Hospitals of North Midlands NHS Trust
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B15 2GW

Study participating centre
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Study participating centre
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Study participating centre
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MK6 5LD

Study participating centre
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AB15 6RE

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
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High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
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LS9 7TF

Sponsor information

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Sponsor details
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United Kingdom

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Sponsor type
Hospital/treatment centre

Website
http://www.birmingham.ac.uk/index.aspx

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Cure Leukaemia

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication of results in peer-reviewed scientific journals and dissemination through an internal report, conference presentation, and publication on the study website.

The local Investigators will be notified when the results are published. They are in a position to contact the patients, if the patients wish to be contacted, and relay the information in an easily comprehensible form. The study website will also have a section for patients where details of the results can be accessed.

Intention to publish date
31/03/2024

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.0		11/02/2022	No	Yes
Participant information sheet	version 7.0	07/12/2021	11/02/2022	No	Yes
Participant information sheet	version 3.0	07/12/2021	11/02/2022	No	Yes
HRA research summary			28/06/2023	No	No
Basic results		18/07/2024	30/07/2024	No	No