Study Protocol C1-001

01/11/2022

Version 2.0

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DOCUMENT HISTORY

Version	Date	Description
V1.0	01/09/2022	**First submission to EMA**
V2.0	01/11/2022	**Update incorporating EMA feedback after approval**

Study Title	Prevalence of rare blood cancers in Europe
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Date of last version of protocol	01/11/2022
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Active substance	N/A
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Research question andobjectives	Research question What is the prevalence of rare blood cancers in Europe? Study objectives Objective 1: To estimate the prevalence of follicular lymphoma between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex Objective 2: To estimate the prevalence of diffuse Large B-Cell Lymphoma between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex Objective 3: To estimate the prevalence of multiple myeloma between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex Objective 4: To estimate the prevalence of chronic lymphocytic leukaemia between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex Objective 5: To estimate the prevalence of acute myeloid leukaemia between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex and sex Objective 6: To estimate the prevalence of acute lymphocytic leukaemia between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex
Country(-ies) of study	The Netherlands, Spain, United Kingdom, Belgium, and Germany

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LIST OF ABBREVIATIONS

Acronyms/terms	Description
Point prevalence	Total number of individuals with an outcome of interest at a particular time divided by the population at risk of having the outcome at that time
Period prevalence	Total number of individuals with an outcome of interest during a particular period divided by the population at risk of having the outcome during the period
Complete prevalence	In complete prevalence outcome events are considered to persist indefinitely. That is, regardless of how long ago an individual had the event, the person remains as a prevalent case.
Partial prevalence	In partial prevalence outcome events are considered to persist for a fixed amount of time following an initial diagnosis. That is, to be a prevalent case at a given time, an individual must have had the outcome observed for the first time during a fixed time in the past (e.g. 5 years).

1. TITLE

Prevalence of rare blood cancers in Europe

2. RESPONSIBLE PARTIES – STUDY TEAM

Study team Role	Names	Organisation
Principal Investigator	Dr. Edward Burn Dr. Martí Català Sabaté	University of Oxford University of Oxford
Epidemiologist	Dr. Albert Prats-Uribe Dr. Annika Jödicke	University of Oxford University of Oxford
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3. ABSTRACT

Title

Prevalence of rare blood cancers in Europe

Rationale and Background

Substantial uncertainty surrounds the prevalence of rare blood cancers. Using real-world data, brought together as part of DARWIN EU®, we aim to estimate the prevalence of rare blood cancers in order to see if they still meet the condition to be classified as a rare disease.

Research question and Objectives

Research question

What is the prevalence of rare blood cancers in Europe?

Study objectives

Objective 1: To estimate the prevalence of follicular lymphoma between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex

Objective 2: To estimate the prevalence of diffuse Large B-Cell Lymphoma between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex

Objective 3: To estimate the prevalence of multiple myeloma between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex

Objective 4: To estimate the prevalence of chronic lymphocytic leukaemia between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex

Objective 5: To estimate the prevalence of acute myeloid leukaemia between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex

Objective 6: To estimate the prevalence of acute lymphocytic leukaemia between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex

Research Methods

Study design

Population-based cohort

Population

All people in a database will be eligible for inclusion in the study. Included study participants will need to have some observation time during the study period and, for the primary analysis, have a year of prior history available. In sensitivity analyses the requirement for prior history will first be removed, and then increased to three years.

Variables

Two age groupings will be used in the study: 1) 0-9; 10-19; 20-29; 30-39; 40-49; 50-59; 60-69; 70-79; 80-89; 90-99; 100+, and 2) 0-44; 45-64; 65 and over. The sex (male/ female) of study participants will also be identified.

Study outcomes will be identified based on the presence of a relevant diagnosis or observation. For the primary analysis, 5-year partial prevalence will be estimated and so individuals will be considered as a prevalent case if they have had their first diagnosis in the prior 5 years. In sensitivity analyses, 2-year partial prevalence and complete prevalence will be estimated. For the latter, once identified as a case, an individual will remain so until their exit from the study (i.e. considering people diagnosed with malignancies to always be affected by the condition).

Data sources

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. The Clinical Practice Research Datalink (CPRD) GOLD database
4. IQVIA LPD Belgium
5. IQVIA DA Germany

Sample size

No sample size has been calculated as this is a Disease Epidemiology Study where we are interested in the prevalence of haematological cancers in as large and representative a denominator population as possible.

Data analyses

In line with EMA guidelines for the estimation of the prevalence of rare disease, point prevalence will be used for the primary analysis. The prevalence of each outcome of interest calculated on an annual basis as of the 1st January for each year, estimated overall and stratified by age and sex. As a sensitivity analysis annual period prevalence will also be estimated. A minimum cell count of 5 will be used when reporting results, with any smaller counts obscured.

4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
2.0	03/11/2022	All	Update	Updated following EMA assessment.

5. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	1st September 2022
Final Study Protocol	1st November 2022
Creation of Analytical code	To be confirmed
Execution of Analytical Code on the data	To be confirmed
Interim Study Report (if applicable)	To be confirmed
Draft Study Report	To be confirmed
Final Study Report	To be confirmed

6. RATIONALE AND BACKGROUND

The Committee for Orphan Medicinal Products (COMP) is the European Medicines Agency's (EMA) committee responsible for recommending orphan designation of medicines for rare diseases. It was established in 2000 when new legislation was introduced to encourage the development of medicinal products for rare diseases. One important criterion for granting an orphan designation to a medicine is a prevalence threshold of maximum 5 in 10,000 for the associated condition at the time of application. Of the submissions to the COMP, around 35% are for oncological conditions and around 42% of designations of orphan medicinal products in oncology granted by the COMP between 2000 and 2015 related to rare haematological malignancies.[1]

Prevalence estimates, such as of rare haematological malignancies, are a frequent source of uncertainty when submissions to the COMP are being assessed. [2] In particular, limited availability of population-based epidemiological studies has often led to the use of indirect methods for calculations of prevalence which often involves various assumptions. In addition, time trends in prevalence may also be present meaning that certain conditions that previously satisfied the prevalence criterion for orphan designation in the past may no longer do so. Indeed, increased prevalence has previously been noted for a number of rare haematological malignancies, which may be explained by improved survival and aging populations.[1] In this study the prevalence of rare blood cancers will be measured in Europe over time.

7. RESEARCH QUESTION AND OBJECTIVES

What is the prevalence of rare blood cancers in Europe?

Study objectives

Objective 1: To estimate the prevalence of follicular lymphoma between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex

Objective 2: To estimate the prevalence of diffuse Large B-Cell Lymphoma between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex

Objective 3: To estimate the prevalence of multiple myeloma between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex

Objective 4: To estimate the prevalence of chronic lymphocytic leukaemia between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex

Objective 5: To estimate the prevalence of acute myeloid leukaemia between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex

Objective 6: To estimate the prevalence of acute lymphocytic leukaemia between 1st January 2010 and the end of available data in data sources from across Europe, stratified by age and sex

Table 1. Primary research questions and objectives

Objective:	To estimate the prevalence of rare blood cancers (follicular lymphoma, diffuse Large B-Cell Lymphoma, Multiple Myeloma, Chronic Lymphocytic Leukaemia, Acute Myeloid Leukaemia, Acute Lymphocytic Leukaemia)
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	All persons in the selected databases will be eligible for inclusion in the study (for main analysis all patients need to have at least 1 year of database history)
Exposure:	Not applicable
Comparator:	Not applicable
Outcome:	Rare blood cancers: Follicular lymphoma, Diffuse Large B-Cell Lymphoma, Multiple Myeloma, Chronic Lymphocytic Leukaemia, Acute Myeloid Leukaemia, Acute Lymphocytic Leukaemia
Time *(when follow up begins and ends):*	1st January 2010 – end of available data within data sources
Setting:	5 Electronic Health Care Record databases across Europe
Main measure of effect:	Prevalence

8. RESEARCH METHODS

8.1 Study type and Study Design

Population-level descriptive epidemiology within a cohort study. Study design diagrams with description of follow-up are described below. The study will include all people in a database and, for the primary analysis, have a year of prior history available. The prevalence of each outcome of interest calculated on an annual basis as of the 1st January for each year, estimated overall and stratified by age and sex. As a sensitivity analysis annual period prevalence will also be estimated. 5-year partial prevalence will be used for the primary analysis, with individuals will be considered as a prevalent case if they have had their first diagnosis in the prior 5 years. In sensitivity analyses, 2-year partial prevalence and complete prevalence will be estimated. For the latter, once identified as a case, an individual will remain so until their exit from the study.

8.2 Study Setting and Data Sources

Integrated Primary Care Information Project (IPCI), The Netherlands (Erasmus)

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands. The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996. The median follow-up is 2.6 years. The observation period for a patient is determined by the date of registration at the GP and the date of exit/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. [3]

Information System for Research in Primary Care (SIDIAP), Spain (IDIAP Jordi Gol)

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database.[4]

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). Data are available for 20 million patients, including 3.2 million currently registered patients. [5]

IQVIA Longitudinal Patient Database (LPD) Belgium

IQVIA LPD Belgium is a computerised network of GPs who contribute to a centralised database of anonymised data of patients with ambulatory visits. Currently, around 300 GPs from 234 practices are contributing to the database covering 1.1M patients from a total of 11.5M Belgians (10.0%). The database covers time from 2005 through the present. Observation time is defined by the first and last consultation dates.

IQVIA Disease Analyser (DA) Germany

IQVIA Disease Analyser (DA) Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings. Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patients have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices.

Table 2. Description of the selected Data Sources.

Country	Name of Database	Justification for Inclusion	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects
The Netherlands	Integrated Primary Care Information Project (IPCI)	Database selected for Y1 of Darwin EU® and has information on blood cancers	Primary care	EHR	1.4 million
Spain	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP)	Database selected for Y1 of Darwin EU® and has information on blood cancers	Primary care with hospital linkage	EHR	5.8 million
United Kingdom	The Clinical Practice Research Datalink (CPRD) GOLD database	Database selected for Y1 of Darwin EU® and has information on blood cancers	Primary care	EHR	3 million
Belgium	IQVIA Belgium	Database selected for Y1 of Darwin EU® and has information on blood cancers	Ambulatory EMR (GP + SP)	EHR	435,200

Country	Name of Database	Justification for Inclusion	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects
Germany	IQVIA DA Germany	Database selected for Y1 of Darwin EU® and has information on blood cancers	Ambulatory EMR (GP + SP)	EHR	8.5 million

ALL: acute lymphocytic leukaemia, AML: acute myeloid leukaemia, CLL: chronic lymphocytic leukaemia, MM: multiple mieloma, DLBCL: diffuse Large B-Cell Lymphoma, FNHL: follicular lymphoma

8.3 Study Period

The study period will be between 1st January 2010 and the end of available data in each of the data sources.

8.4 Follow-up

Study participants will begin contributing person time on the respective date of the latest of the following: 1) study start date (1st January 2010), 2) date at which they have sufficient prior history (365 days, or if there is no requirement for prior history this date will coincide with the date at which their observation period starts), 3) date at which they reach a minimum age (where age strata are being considered). Participants will stop contributing person time at the earliest date of the following: 1) study end date (end of available data in each of the data sources), 2) date at which their observation period ends, 3) the last day in which they have the maximum age (where age strata are being considered). Where there are multiple age strata, study participants will contribute to each strata while they satisfy the conditions of that strata (i.e. when they reach the limit of one age strata they will begin contributing to the next).

An overview of study entry and exit is shown below in **Figure 1** for the overall analysis, with entry of exit for a given age strata shown in **Figure 2**. In this latter example person ID 1 and 3 enter the study on the day they reach the minimum age and exits at the study end date. Person ID 2 enters the study on the study start date and exits at the maximum age. Person ID 4 enters the study on the day they reach the minimum age and leaves when they exit the database (the end of their observation period). Person ID 5 enters the study on the day they have sufficient prior history and exits at the study end date. Lastly, person ID 6 has two observation periods in the database. For the first they enter and contribute time until their exit, for the second they start contributing time again once they have sufficient prior history and exit at the maximum age.

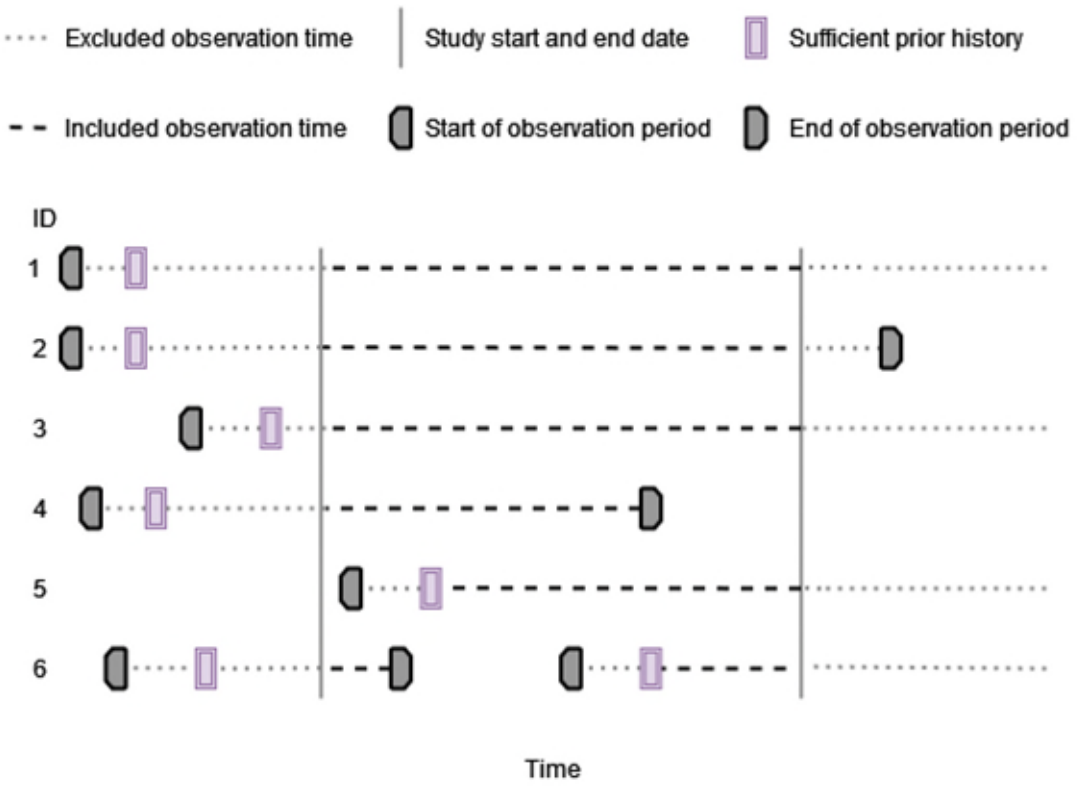

Figure 1 Included observation time for study participants overall

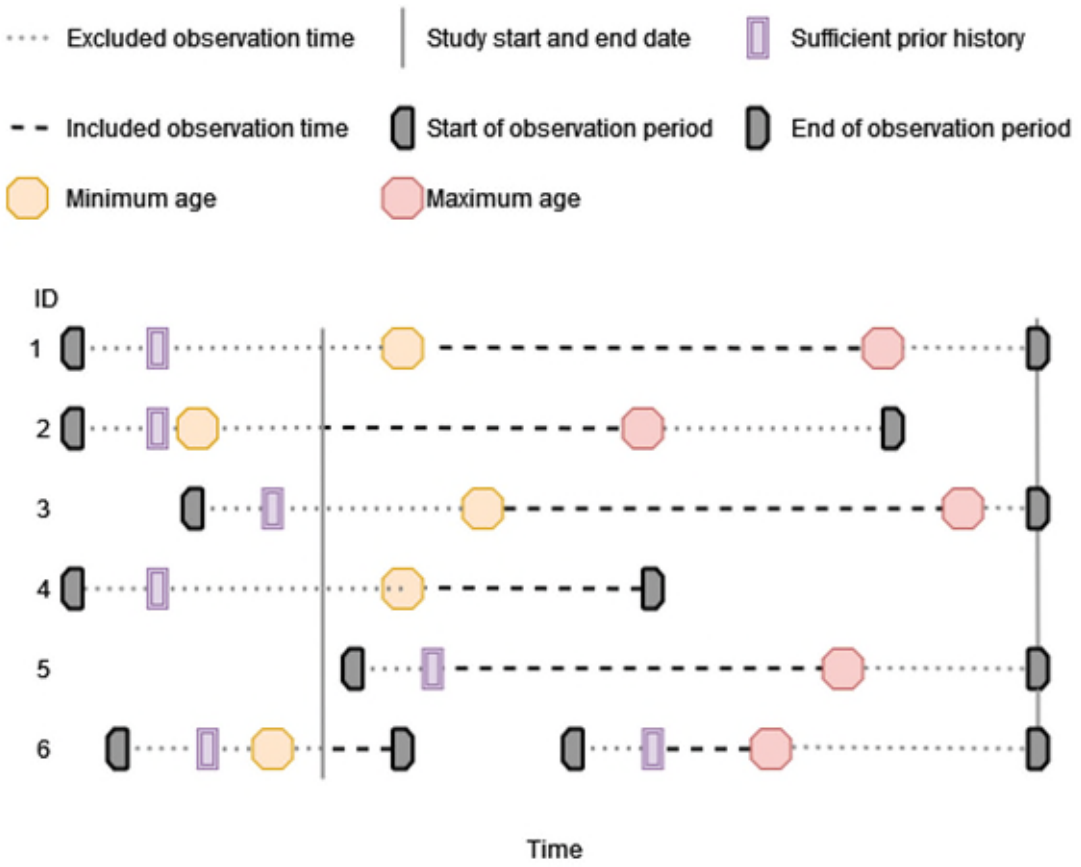

Figure 2. Included observation time for study participants for a given age strata

8.5 Study Population with inclusion and exclusion criteria

All persons in a database will be eligible for inclusion in the study. They will though only enter the study if they have some observation time during the study period. For the primary analysis, study participants will be required to have a year of prior history observed before contributing observation time. This is to ensure a minimum prior observation time to identify any ongoing outcomes (i.e. rare blood cancer) at the time at which a participant enters the study. In sensitivity analyses the requirement for prior history will first be removed, and then increased to three years.

Table 3. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Prior database history	Study participants will be	After	1 year	Primary care and combination of	N/A	N/A	All individuals within the	N/A	N/A

of 1 year	required to have a year of prior history observed before contributing observation time			primary and secondary care for IQVIA Germany			selected databases		

* After as first possible study entry date is selected and then it is checked whether patient has one year of database history. In a sensitivity analysis, this rule will be removed. In another sensitivity analysis, required history will be increased to 3 years. N/A: not applicable for this study or data sources being used

8.6 Variables

8.6.1. Exposure/s (where relevant)

N/A as no specific drugs of interests are investigated.

8.6.2. Outcome/s (where relevant)

Outcome cohort definitions for partial and complete prevalence

Complete prevalence represents the number of persons alive at the specific point in time regardless of how long ago the diagnosis was, while partial prevalence limits the number of patients to those diagnosed during a fixed time in the past.[6] To operationalise this definition outcome cohorts will be defined which vary in how the cohort exit is defined. For complete prevalence an individual will remain in the outcome cohort until the end of their observed time at risk. Meanwhile, for partial prevalence, an individual will exit the outcome cohort after a certain number of days has elapsed since the first record indicating them to be a prevalent case (e.g. 1,825 days for 5-year partial prevalence).

Follicular lymphoma

Follicular lymphomas are the second leading Non-Hodgkin's lymphomas and can be diagnosed accurately on morphologic findings alone: B-cell in follicular centre. Many patients are diagnosed incidentally or at a time when their lymphoma is not causing symptoms or signs of organ function impairment. The major differential diagnosis is between lymphoma and reactive follicular hyperplasia. The coexistence of diffuse large B-cell lymphoma must be considered. Patients with follicular lymphomas are often subclassified, or graded, into those with predominantly small cells, those with a mixture of small and large cells, and those with predominantly large cells. The typical natural history is a pattern of continuous relapses with a diminishing sensitivity to chemotherapy. On average, most patients will live with follicular lymphoma for 15 to 20 years.

For this study, cases will be identified based on a record indicating a diagnosis or observation of follicular lymphoma. A clinical description along with a preliminary code list is provided in Appendix 1. For the primary analysis, 5-year partial prevalence will be estimated and so individuals will be considered as a prevalent case if they had a relevant record observed in the prior 1,825 days. In sensitivity analyses, 2-year partial prevalence

will be estimated (using records in the prior 730 days) as will complete prevalence. For the latter, individuals will continue to be considered as a prevalent case from their first observed diagnosis or observation of follicular lymphoma up until the end of their observation time.

Diffuse Large B-Cell Lymphoma

Diffuse Large B-Cell Lymphoma is the most common Non-Hodgkin lymphoma, accounting for about 1 in 3 of these conditions. Diffuse Large B-Cell Lymphoma is also more common in people with a family history and in the immuno-compromised (individuals on immune suppressive therapy or with a condition like HIV or EBV-related). It is common for diffuse Large B-Cell Lymphoma to be diagnosed at an advanced stage, with involvement of bone marrow, CNS, GI, thyroid, liver, and/or skin.

For this study, cases will be identified based on a record indicating a diagnosis or observation of large B-Cell lymphoma. A clinical description along with a preliminary code list is provided in Appendix 1. For the primary analysis, 5-year partial prevalence will be estimated and so individuals will be considered as a prevalent case if they had a relevant record observed in the prior 1,825 days. In sensitivity analyses, 2-year partial prevalence will be estimated (using records in the prior 730 days) as will complete prevalence. For the latter, individuals will continue to be considered as a prevalent case from their first observed diagnosis or observation of large B-Cell lymphoma up until the end of their observation time.

Multiple myeloma

Multiple myeloma is a malignant uncontrolled proliferation of plasma cells derived from one single clone. Multiple myeloma can affect many organs, typically bones and calcium metabolism, kidneys, immune system, blood, and more rarely neurologic. Diagnosis is typically obtained after bone marrow biopsy, where plasma cells, monoclonal kappa or lambda light chains will be present. The most important differential diagnosis is monoclonal gammapathy of unknown significance (MGUS) or 'smoldering multiple myeloma'.

For this study, cases will be identified based on a record indicating a diagnosis or observation of multiple myeloma. A clinical description along with a preliminary code list is provided in Appendix 1. For the primary analysis, 5-year partial prevalence will be estimated and so individuals will be considered as a prevalent case if they had a relevant record observed in the prior 1,825 days. In sensitivity analyses, 2-year partial prevalence will be estimated (using records in the prior 730 days) as will complete prevalence. For the latter, individuals will continue to be considered as a prevalent case from their first observed diagnosis or observation of multiple myeloma up until the end of their observation time.

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia is a neoplasm characterised by the proliferation and accumulation of lymphocytes, usually B lineage, immune-incompetent. It is characterised by an invasion of peripheral and medullary blood by lymphocytes, and is of low aggressiveness. In most cases it presents asymptomatically (incidental finding of lymphocytosis). The clinical manifestations of this disease are due to the progressive infiltration of the bone marrow, lymph nodes and other tissues by lymphocytes, and to immunological alterations. Chronic lymphocytic leukaemia is a very common entity, especially in elderly patients. Therefore, in the presence of lymphocytosis with conclusive flow cytometry in peripheral blood, the diagnosis is a fact and no further complementary studies will be required if the patient is asymptomatic and has no treatment criteria. Carrying out more complex diagnostic techniques such as bone marrow biopsy, mutation studies, cytogenetics or imaging tests are only justified if the patient is symptomatic or meets treatment criteria.

For this study, cases will be identified based on a record indicating a diagnosis or observation of chronic lymphocytic leukaemia. A clinical description along with a preliminary code list is provided in Appendix 1. For the primary analysis, 5-year partial prevalence will be estimated and so individuals will be considered as a

prevalent case if they had a relevant record observed in the prior 1,825 days. In sensitivity analyses, 2-year partial prevalence will be estimated (using records in the prior 730 days) as will complete prevalence. For the latter, individuals will continue to be considered as a prevalent case from their first observed diagnosis or observation of chronic lymphocytic leukaemia up until the end of their observation time.

Acute myeloid leukaemia

Acute myeloid leukemia is the most common acute leukemia in older patients. Characterised by the infiltration of blood, bone marrow and sometimes other tissues by proliferative, poorly differentiated hematopoietic cells. Mostly presenting with nonspecific symptoms that begin gradually, or abruptly, and are the consequence of anemia, leukocytosis, leukopenia/leukocyte dysfunction, or thrombocytopenia, typically up to 3 months before diagnosis. Long-term survival is infrequent, at about 1 in 4 in 5 years from diagnosis.

For this study, cases will be identified based on a record indicating a diagnosis or observation of acute myeloid leukaemia. A clinical description along with a preliminary code list is provided in Appendix 1. For the primary analysis, 5-year partial prevalence will be estimated and so individuals will be considered as a prevalent case if they had a relevant record observed in the prior 1,825 days. In sensitivity analyses, 2-year partial prevalence will be estimated (using records in the prior 730 days) as will complete prevalence. For the latter, individuals will continue to be considered as a prevalent case from their first observed diagnosis or observation of acute myeloid leukaemia up until the end of their observation time.

Acute lymphocytic leukaemia

Acute lymphocytic leukaemia is a type of cancer that affects white blood cells. In acute lymphocytic leukaemia, the process of development of blood cells is faulted, with immature, non-functioning leukemic cells being released from hematopoietic progenitors in the bone marrow or lymphatic system. This leads to anaemia, granulocytopenia, and thrombocytopenia, and causes symptoms of fatigue, weakness, breathlessness, infection, and haemorrhage. Common symptoms when patients first seek medical advice include fatigue and feeling breathless, repeated infections over a short time and unusual and frequent bleeding. Other symptoms can comprise pale, easily bruised skin; high temperature and night sweats; bone and joint pain as well as swollen lymph nodes, abdominal pain and unintentional weight loss. In some cases the central nervous system is also affected, with neurological symptoms including headaches, seizures, blurred vision or dizziness being reported. Acute lymphocytic leukaemia generally progresses quickly and aggressively, with immediate treatment being required. Prognosis is highly age-related, with cure rates of around 90% in children, decreasing to <10% in elderly or frail patients

For this study, cases will be identified based on a record indicating a diagnosis or observation of acute lymphocytic leukaemia. A clinical description along with a preliminary code list is provided in Appendix 1. For the primary analysis, 5-year partial prevalence will be estimated and so individuals will be considered as a prevalent case if they had a relevant record observed in the prior 1,825 days. In sensitivity analyses, 2-year partial prevalence will be estimated (using records in the prior 730 days) as will complete prevalence. For the latter, individuals will continue to be considered as a prevalent case from their first observed diagnosis or observation of acute lymphocytic leukaemia up until the end of their observation time.

Table 4. Operational definition of the different outcomes

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings [1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
Follicular lymphoma	For clinical description of outcome, see above	Yes	Binary	N/A	Primary care and combination of primary and secondary care for IQVIA Germany	SNOMED	N/A	All individuals within the selected databases	N/A	N/A
Diffuse Large B-Cell Lymphoma	For clinical description of outcome, see above	Yes	Binary	N/A	Primary care and combination of primary and secondary care for IQVIA Germany	SNOMED	N/A	All individuals within the selected databases	N/A	N/A
Multiple myeloma	For clinical description of outcome, see above	Yes	Binary	N/A	Primary care and combination of primary and secondary care for IQVIA Germany	SNOMED	N/A	All individuals within the selected databases	N/A	N/A
Chronic lymphoc	For clinical	Yes	Binary	N/A	Primary care and	SNOMED	N/A	All individu	N/A	N/A

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings [1]	Code Type [2]	Diagnosis Position [3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
ytic leukaemia	description of outcome, see above				combination of primary and secondary care for IQVIA Germany			als within the selected databases		
Acute myeloid leukaemia	For clinical description of outcome, see above	Yes	Binary	N/A	Primary care and combination of primary and secondary care for IQVIA Germany	SNOMED	N/A	All individuals within the selected databases	N/A	N/A
Acute lymphocytic leukaemia	For clinical description of outcome, see above	Yes	Binary	N/A	Primary care and combination of primary and secondary care for IQVIA Germany	SNOMED	N/A	All individuals within the selected databases	N/A	N/A

N/A: not applicable for this study or data sources being used

8.6.3. Other covariates, including confounders, effect modifiers and other variables (where relevant)

Two age groupings will be used: 1) 0-9; 10-19; 20-29; 30-39; 40-49; 50-59; 60-69; 70-79; 80-89; 90-99; 100+, and 2) 0-44; 45-64; 65 and over. The latter, broader, age groups will be used where low counts preclude reporting results for the 10-year age bands. The sex (male/ female) of study participants will also be identified.

8.7 Study size

No sample size has been calculated as this is a Disease Epidemiology Study where we are interested in the prevalence of haematological cancers in the entire population.

8.8 Analysis

Prevalence summarises the total number of individuals who have the outcome of interest at a particular time or during a particular period divided by the population at risk of having the outcome at that time or during the period. Point prevalence gives the proportion of individuals in a population who have the outcome at a given point in time, while period prevalence gives the proportion of individuals with the outcome at any time during a specified time period or interval. A key aspect here is that an outcome is defined in the sense of having a duration, with a start and an end date. As mentioned above, in partial prevalence the outcome end date is determined by a fixed number of days since the first record of the outcome event whereas in complete prevalence the outcome end date is defined as the end of observation time for an individual who has at some point prior had a record of the outcome.

For an example of calculations of point and period prevalence under partial prevalence see **Figure 3** below. It can be seen that at time t+2, two of the five study participants are in an outcome cohort giving a point prevalence of 40%. Period prevalence between t+2 and t+3 in this simple example would give the same answer. However, for the period t to t+1 the result will depend on whether study participants are required to have been observed for the full study period. If no such restriction is imposed all five study participants would contribute, but if study participants had to have been observable for the full period, then only three of the study participants would contribute.

In this study the primary analysis will use point prevalence, estimated as of the 1st January of each calendar year. We will also estimate period prevalence as a sensitivity analysis, estimated on an annual basis (between the 1st January and 31st December for each year). Period prevalence will first be estimated with participants required to contribute a minimum of only one day of the period to be included. Subsequently, we will estimate period prevalence with participants required to be observed for the full period for them to be included.

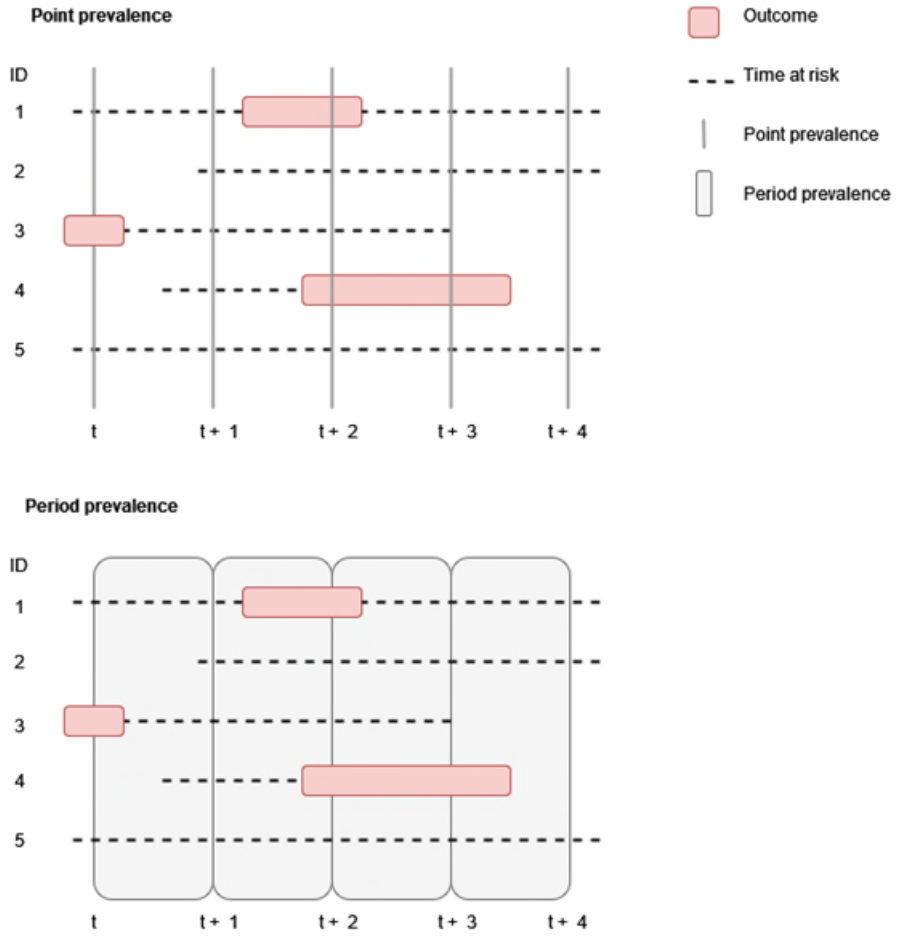

Figure 3. Point and period prevalence

A summary of the analyses being performed in the study are detailed below in **Table 5**. As mentioned above, these analyses vary based on prevalence type (primary: 5-year partial prevalence, sensitivity: 2-year partial prevalence, and complete prevalence), 2) prevalence estimate (primary: point prevalence, sensitivity: period prevalence), 3) prior history requirement for study population (primary: 365 days, sensitivity: 0 and 1,095 days), 4) observable time requirement for period prevalence (primary: not applicable, sensitivity: one day and full period year).

Table 5. Summary of analysis settings

Analysis	Type	Prevalence estimate	Study population: prior history required before contributing follow up time	Observable time required for time period (period prevalence only)
*5-year partial prevalence**				
1	Primary	Point prevalence	365 days	N/A
2	Sensitivity	Period prevalence (annual)	365 days	One day
3	Sensitivity	Period prevalence (annual)	365 days	Full year
4	Sensitivity	Point prevalence	0 days	N/A
5	Sensitivity	Period prevalence (annual)	0 days	One day
6	Sensitivity	Period prevalence (annual)	0 days	Full year
6	Sensitivity	Point prevalence	1095 days	N/A
7	Sensitivity	Period prevalence (annual)	1095 days	One day
8	Sensitivity	Period prevalence (annual)	1095 days	Full year
2-year partial prevalence†				
9	Sensitivity	Point prevalence	365 days	N/A
10	Sensitivity	Period prevalence (annual)	365 days	One day
11	Sensitivity	Period prevalence (annual)	365 days	Full year
12	Sensitivity	Point prevalence	0 days	N/A
13	Sensitivity	Period prevalence (annual)	0 days	One day
14	Sensitivity	Period prevalence (annual)	0 days	Full year
15	Sensitivity	Point prevalence	1095 days	N/A
16	Sensitivity	Period prevalence (annual)	1095 days	One day
17	Sensitivity	Period prevalence (annual)	1095 days	Full year
Complete prevalence‡				
18	Sensitivity	Point prevalence	365 days	N/A
19	Sensitivity	Period prevalence (annual)	365 days	One day

Analysis	Type	Prevalence estimate	Study population: prior history required before contributing follow up time	Observable time required for time period (period prevalence only)
20	Sensitivity	Period prevalence (annual)	365 days	Full year
21	Sensitivity	Point prevalence	0 days	N/A
22	Sensitivity	Period prevalence (annual)	0 days	One day
23	Sensitivity	Period prevalence (annual)	0 days	Full year
24	Sensitivity	Point prevalence	1095 days	N/A
25	Sensitivity	Period prevalence (annual)	1095 days	One day
26	Sensitivity	Period prevalence (annual)	1095 days	Full year

*For 5-year partial prevalence individuals will be considered as a prevalent case if they had their initial diagnosis observed in the prior 1,825 days. *For 2-year partial prevalence will be considered as a prevalent case if they had a relevant record observed in the prior 730 days. ‡For complete prevalence individuals will be considered as a prevalent case if they have ever had a relevant record previously.

8.9 Evidence synthesis

Results will be presented separately by database.

9. DATA MANAGEMENT

All databases will have been mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

This analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

10. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values.[7] Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining outcomes, a systematic search of possible codes for inclusion will be identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. The codes returned will then be reviewed by two clinical epidemiologist to consider their relevance. In addition, the CohortDiagnostics R package (https://github.com/OHDSI/CohortDiagnostics) will be run to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This will allow for a consideration of the validity of the outcome cohorts in each of the databases, and inform decisions around whether multiple definitions are required (e.g. broad and narrow definition may be defined if there are some frequently used codes that are not particularly precise).

The study code will be based on an R package currently being developed to estimate Incidence and Prevalence using the OMOP common data model. This package will include numerous automated unit tests to ensure the validity of the code, alongside software peer review and user testing. This R package will be made publicly available via GitHub.

11. LIMITATIONS OF THE RESEARCH METHODS

The study will be informed by routinely collected health care data and so data quality issues must be considered. In particular, the recording of the outcome events may vary across databases and while relatively few false positives would be expected, false negatives may be more likely especially for databases without patient-level linkage to secondary care data. In addition, assumptions around the duration of outcomes will be unavoidable. While we will consider partial prevalence over two different periods (2-year and 5-year) these durations are necessarily arbitrary. Similarly, estimates of complete prevalence (where an event is assumed to persist until the end of observation) may include people that could be considered to have recovered from their cancer.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the guideline on good pharmacovigilance practice (EMA/873138/2011 Rev 2*) there is no requirement for expedited reporting of adverse drug reactions from studies with secondary use of data (such as electronic health care databases).

13. GOVERNANCE BOARD ASPECTS

SIDIAP, IPCI, and CPRD will require ethical approvals to perform this study. IQVIA Belgium and IQVIA DA Germany will not require any further specific approvals to undertake this study.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Dissemination activities to be undertaken will have mainly, although not exclusively, a scientific nature (articles, presentations at conferences, etc.).

15. OTHER ASPECTS

N/A

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17. ANNEXES

Appendix I: Definitions of study outcomes

Follicular lymphoma

Clinical description

Overview

FLs are the second leading Non-Hodgkin's lymphomas (NHL), makes up 22% of NHL worldwide. This type of lymphoma can be diagnosed accurately on morphologic findings alone: B-cell in follicular centre.
Confirmation of B-cell immunophenotype (monoclonal immunoglobulin light chain, CD19, CD20, CD10 and BCL6 positive, and CD5 and CD23 negative) and the existence of the t(14;18) and abnormal expression of BCL-2 protein are confirmatory (85%).

The major differential diagnosis is between lymphoma and reactive follicular hyperplasia. The coexistence of DLBCL must be considered. Patients with FL are often subclassified, or graded, into those with predominantly small cells, those with a mixture of small and large cells, and those with predominantly large cells.

Presentation

Presentation for FL is with new, painless lymphadenopathy. Multiple sites of lymphoid involvement are typical, and unusual sites such as epitrochlear nodes are sometimes seen. However, essentially any organ can be involved, and extranodal presentations do occur. Many of these patients are diagnosed incidentally or at a time when their lymphoma is not causing symptoms or signs of organ function impairment
Most patients do not have an elevated LDH or fevers, night sweats, or weight loss (<20%). Transformation to DLBCL does occur at a rate of ~3% per year and can be associated with these signs/symptoms.

Assessment

Diagnosis: Lymph node biopsy.
Staging is typically done with CT scans of the chest, abdomen and pelvis, as well as the neck if neck disease is suspected, although PET/CT scans can be helpful in cases where disease transformation is suspected.

Grading

The WHO Classification adopted grading from 1 to 3 based on the number of centroblasts, or large cells, counted per high power field (hpf):
grade I, from 0 to 5 centroblasts/hpf;
grade II, from 6 to 15 centroblasts/hpf;
grade III, >15 centroblasts/hpf.
Grade III has been subdivided into grade IIIa, in which centrocytes predominate, and grade IIIb, in which there are sheets of centroblasts.
While this distinction cannot be made simply or very reproducibly, these subdivisions do have prognostic significance. Grade IIIb FL is an aggressive disease and considered most similar to Diffuse large B-cell lymphoma (DLBCL) and treated as such with curative intent.

Plan

- observation
  Reasonable alternative. Numerous studies have shown that treating patients with asymptomatic disease does not improve survival compared with a program of close observation with treatment reserved for symptomatic disease progression or organ dysfunction
- radiotherapy
  Although FL is highly sensitive to chemotherapy and radiotherapy, these therapies are usually not ultimately curative, except in the setting of early-stage disease.
- chemotherapy associated with rituximab (R-CHOP, R-Bendamustine) -
  Monoclonal antibody against CD20, [rituximab], alone or its use in combination with chemotherapy.
  Treatment decisions are often determined by the indication for treatment and/or by the volume of disease being treated.
  For patients requiring therapy for inflammatory or autoimmune phenomenon thought to be driven by FL, or for patients with low volume disease, single-agent [rituximab]
  For patients with a larger volume of disease at the time of treatment initiation, the addition of chemotherapy (CHOP, R-CHOP, R-CVP). [cyclophosphamide], [doxorubicin], [vincristine] and [prednisone], improved survival in this disease.
  The combination of [bendamustine], [rituximab] [R-CHOP] longer response duration and less toxicity.
  BR then has become the standard of care for the first-line therapy of medium to high-volume FL.
  Similarly, the addition of maintenance [rituximab] improves response duration when used in newly treated FL patients.
- Autologous and allogeneic hematopoietic stem cell transplantation yield high complete response -
- Targeted oral therapies like [lenalidomide] and the PI3 kinase inhibitor [idelalisib]

Prognosis

The typical natural history is a pattern of continuous relapses with a diminishing sensitivity to chemotherapy. On average, most patients will live with FL for 15–20 years.

May return spontaneously but partially and temporarily.

Can transform into a High-grade lymphoma (more aggressive) with poor prognosis in 20% of patients, (~3% per year). rapid growth of lymph nodes and the development of systemic B-symptoms. They have sometimes been described spontaneous remissions.

Prognostic scale: https://www.mdcalc.com/calc/2320/follicular-lymphoma-international-prognostic-index-flipi

Preliminary code list

Condition domain

concept_id	concept_name
35610325	Follicular lymphoma, cutaneous follicle centre
4002357	Follicular non-Hodgkin's lymphoma, small cleaved cell (clinical)
4001329	Follicular non-Hodgkin's lymphoma, mixed small cleaved cell and large cell (clinical)
4003833	Follicular non-Hodgkin's lymphoma, large cell (clinical)
4097572	Follicular non-Hodgkin's mixed small cleaved and large cell lymphoma
4079288	Follicular low grade B-cell lymphoma
4173977	Follicular malignant lymphoma - mixed cell type
4079289	Follicular malignant lymphoma - small cleaved cell
4123298	Malignant lymphoma, follicular center cell
4121853	Malignant lymphoma, follicular center cell, cleaved
4121970	Malignant lymphoma, follicular center cell, non-cleaved
4146630	Malignant lymphoma, centroblastic-centrocytic, follicular
4141258	Malignant lymphoma, centroblastic type, follicular
4147411	Follicular non-Hodgkin's lymphoma
36684826	Follicular non-Hodgkin's lymphoma of lymph nodes of multiple sites
4301668	Primary cutaneous follicular center B-cell lymphoma
4299152	Follicular center B-cell lymphoma (nodal/systemic with skin involvement)
40488901	Follicular non-Hodgkin's lymphoma of prostate
40488917	Follicular non-Hodgkin's lymphoma of nose
40489407	Follicular non-Hodgkin's lymphoma of soft tissue
40490467	Follicular non-Hodgkin's lymphoma of extranodal site
40490991	Follicular non-Hodgkin's lymphoma of bone
40490998	Follicular non-Hodgkin's lymphoma of lung
40492018	Follicular non-Hodgkin's lymphoma of skin
40492940	Follicular non-Hodgkin's lymphoma of central nervous system
40493011	Follicular non-Hodgkin's lymphoma of tonsil
40493012	Follicular non-Hodgkin's lymphoma of uterine cervix
40493017	Follicular non-Hodgkin's lymphoma of oral cavity
40486169	Follicular non-Hodgkin's lymphoma of nasopharynx
40486173	Follicular non-Hodgkin's lymphoma of stomach
40486654	Follicular non-Hodgkin's lymphoma of ovary
40487141	Follicular non-Hodgkin's lymphoma of testis
40487142	Follicular non-Hodgkin's lymphoma of intestine
45765770	Follicular non-Hodgkin's lymphoma diffuse follicle center sub-type grade 1
45765919	Follicular non-Hodgkin's lymphoma diffuse follicle center cell sub-type grade 2
36715795	Follicular lymphoma of small intestine
42537145	Pediatric follicular lymphoma

44808015	Follicular lymphoma grade 1
44814156	Follicular lymphoma grade 2
44808028	Follicular lymphoma grade 3
44808117	Follicular lymphoma grade 3a
44808118	Follicular lymphoma grade 3b
4146024	Malignant lymphoma - centrocytic
4119131	Nodular malignant lymphoma, lymphocytic - well differentiated
4121331	Nodular malignant lymphoma, lymphocytic - intermediate differentiation
4146027	Malignant lymphoma, mixed lymphocytic-histiocytic, nodular
4146031	Malignant lymphoma, lymphocytic, poorly differentiated, nodular
438698	Malignant lymphoma of lymph nodes of head, face AND/OR neck
435753	Malignant lymphoma of intrathoracic lymph nodes
200349	Malignant lymphoma of intra-abdominal lymph nodes
441521	Malignant lymphoma of lymph nodes of axilla AND/OR upper limb
192560	Malignant lymphoma of lymph nodes of inguinal region AND/OR lower limb
195195	Malignant lymphoma of intrapelvic lymph nodes
200343	Malignant lymphoma of spleen
132841	Malignant lymphoma of lymph nodes of multiple sites
435492	Nodular lymphoma of intrathoracic lymph nodes
200338	Nodular lymphoma of intra-abdominal lymph nodes
198088	Nodular lymphoma of intrapelvic lymph nodes
198374	Nodular lymphoma of spleen
320347	Nodular lymphoma of lymph nodes of multiple sites
440058	Malignant lymphoma of extranodal AND/OR solid organ site
194878	Nodular lymphoma of extranodal AND/OR solid organ site
4038838	Non-Hodgkin's lymphoma (clinical)
4149840	Nodular lymphoma

Observation domain

concept_id	concept_name
4017277	Malignant lymphoma, follicular AND/OR nodular
4200880	Follicular low grade B-cell lymphoma morphology
4265301	Follicular lymphoma, cutaneous follicle center sub-type
4265735	Follicular lymphoma, diffuse follicle center sub-type, grade 1
4288232	Follicular lymphoma, diffuse follicle center cell sub-type, grade 2
4230587	Follicular lymphoma, grade 3
4188203	Follicular lymphoma, grade 1
4204524	Follicular lymphoma, grade 2
4205271	Follicular lymphoma
37116892	Pediatric follicular lymphoma
37203899	Nodal peripheral T-cell lymphoma with T follicular helper phenotype

37205181	Follicular T-cell lymphoma
44806990	Follicular lymphoma grade 3a
44806991	Follicular lymphoma grade 3b

Diffuse Large B-Cell Lymphoma

Clinical description

Overview

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common Non-Hodgkin lymphoma, accounting for about 1 in 3 of these conditions. It is slightly more common in white men, and typically diagnosed in the 60s. DLBCL is also more common in people with a family history and in the immuno-compromised (on immune suppresive therapy or with a condition like HIV or EBV-related). It is common for DLBCL to be diagnosed at an advanced stage, with involvement of bone marrow, CNS, GI , thyroid, liver, and/or skin. Common treatments include combination chemotherapy (CHOP) with potential addition of rituximab, cyclophosphamide, doxorubicin, and prednisone. Methotrexate is sometimes used in intratecal form to prevent or treat CNS dissemination. Radiotherapy is used sometimes as a temporary option. Several new agents have shown some promise in patients with relapsed DLBCL: ibrutinib, lenalidomide, and everolimus.

Presentation

Like any other lymphoma, DLBCL can present as blood changes (eg anaemia or pancytopaenia). Also, 1/3 will present with peripheral symptoms, typically bone marrow, CNS, GI, tyroid, or liver symptoms. Also less common but more for DLBCL vs other lymphoma is cutaneous presentation.

Assessment

This will include bloods, bone marrow biopsy, imaging of brain or bone, endoscopy, or ultrasound scan of thyroid or liver.

Plan

On top of the investigations above (Assessment), treatments will include commonly rituximab, cyclophosphamide, doxorubicin, and prednisone. Radiotherapy will also be common. Less common but still visible sometime will be Methotrexate, ibrutinib, lenalidomide, and everolimus.

Prognosis

40% to 50% resolve but then a similar proportion relapse in the following years and need another course of 2nd line therapy

Disqualifiers

Hodgkin's lymphoma, leukemia

Strengtheners

rituximab, CNS presentation, methotrexate, cutaneous presentation, epstein-barr virus

Preliminary code list

Condition domain

concept_id	concept_name
4297358	Primary cutaneous diffuse large cell B-cell lymphoma
4300704	Diffuse large B-cell lymphoma (nodal/systemic with skin involvement)
37399015	Epstein-Barr virus positive diffuse large B-cell lymphoma of elderly
36716774	B-cell lymphoma unclassifiable with features intermediate between Burkitt lymphoma and diffuse large B-cell lymphoma
36716775	B-cell lymphoma unclassifiable with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma
37110401	Diffuse large B-cell lymphoma co-occurrent with chronic inflammation caused by Epstein-Barr virus
37116982	Diffuse large B-cell lymphoma of central nervous system
42539527	Primary cutaneous diffuse large cell B-cell lymphoma of lower extremity
3654886	Diffuse large B-cell lymphoma of small intestine
3654887	Diffuse large B-cell lymphoma of stomach
44808122	Diffuse large B-cell lymphoma
4079293	Diffuse malignant lymphoma - centroblastic polymorphic
4121330	Diffuse malignant lymphoma - centroblastic
4144199	Diffuse malignant lymphoma - centroblastic-centrocytic
4146630	Malignant lymphoma, centroblastic-centrocytic, follicular
4141258	Malignant lymphoma, centroblastic type, follicular
432574	Diffuse non-Hodgkin's lymphoma, large cell (clinical)
764839	Diffuse non-Hodgkin's lymphoma Lugano stage I
4173978	Diffuse malignant lymphoma - large cleaved cell
4079291	Diffuse malignant lymphoma - large non-cleaved cell
4301669	Primary cutaneous anaplastic large cell B-cell lymphoma
4173962	Lymphoma with spill

Observation domain

36712836	B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
36712837	B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Hodgkin lymphoma
4189146	Diffuse large B-cell lymphoma - category
42872963	Malignant lymphoma, diffuse large B-cell, immunoblastic
4262918	Malignant lymphoma, large B-cell, diffuse
37396838	Epstein-Barr virus positive diffuse large B-cell lymphoma of elderly
37116992	Diffuse large B-cell lymphoma associated with chronic inflammation
37117038	B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma

37206914	Diffuse large B-cell lymphoma activated B-cell subtype
37206933	Diffuse large B-cell lymphoma germinal center B-cell subtype
4178883	Malignant lymphoma, mixed small and large cell, diffuse

Multiple myeloma

Clinical description

Overview

Multiple myeloma (MM) is a malignant uncontrolled proliferation of plasma cells derived from one single clone. MM can affect many organs, typically bones and calcium metabolism (e.g. fractures or bone pain, hypercalcemia), kidneys (renal failure/ckd/aki), immune system (e.g. infection), blood (anemia, clotting), and more rarely neurologic.

The etiology of MM is unknown, and it is one of the most common blood cancers, with an estimated incidence rate ranging from 6 to 14/100,000, more common in ages 60-70+ and in ethnic minorities.

Presentation

Bone pain, fractures, and hypercalcemia are the most common manifestations of MM. Radiology would show (on top of fracture/pathologic fracture where present) lytic/osteolytic lesions in plain x-ray or ct scan. Bone lysis results in hypercalcemia, and related complications.
Other typical features that lead to diagnosis include renal failure (ckd or aki) or bacterial infections like pneumonia or pyelonephritis. Recurrent infections are common.
Bloods and urine labs are typically used to investigate/diagnose MM, and will show hypogammaglobulinemia, bence-jones proteins, hypercalcemia, and other alterations of proteinogram.

Assessment

Assessment will typically include imaging e.g. x-ray, ct scan, and sometimes bone gammagraphy or similar techniques. Also, bloods and urine are included often during investigation/diagnosis, typically including full blood counts, biochemistry, immunology, proteinogram, serum electrophoresis, β2Microglobulin, LDH and serum albumin, and bence jones proteins

Diagnosis is typically obtained after bone marrow biopsy, where plasma cells monoclonal kappa or lambda light chains will be present.
The most important differential diagnosis is MGUS (monoclonal gammapathy of unknown significance) or 'smoldering multimple myeloma'. These are far more common than MM, and sometimes preclude or transition to MM proper. It is estimated that about 1% of patients with MGUS transition every year to MM. Patients with MGUS would not have a bone marrow biopsy, but they will/should have repeat bloods over time to monitor/rule out MM.
Diagnostic Criteria
Monoclonal Gammopathy of Undetermined Significance (MGUS)

- Serum monoclonal protein (non-IgM type) <30 g/L
- Clonal bone marrow plasma cells <10%
- Absence of myeloma-defining events or amyloidosis that can be attributed to the plasma cell proliferative disorder

Smoldering Multiple Myeloma (Asymptomatic Myeloma)
Both criteria must be met:
-Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
-Absence of myeloma-defining events or amyloidosis

Symptomatic Multiple Myeloma
Clonal bone marrow plasma cells or biopsy-proven bony or extramedullary plasmacytomaa and any one or more of the following myeloma-defining events:
Evidence of one or more indicators of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance <40 mL/minb or serum creatinine >177 µmol/L (>2 mg/dL)
- Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CTc
- Any one or more of the following biomarkers of malignancy: i.Clonal bone marrow plasma cell percentagea ≥60%; ii.Involved: uninvolved serum free light chain ratiod ≥100; and/or iii.>1 focal lesion on MRI studies

Plan

Common treatments for MM include:

- Immunomodulatory drugs (IMiD) like Thalidomide, Lenalidomide, Pomalidomide
- Proteasome inhibitors (PI) like Bortezomib, Carfilzomib, Ixazomib
- Antibodies/monoclonal antibodies like Daratumumab, Elotuzumab, Isatuximab, Belantamab mafodotin
- Selective inhibitors of nuclear export (SINE) like Selinexor
- Histone deacetylase inhibitors like Panobinostat
- Alkylating agents like Melphalan, Cyclophosphamide, Bendamustine, Melflufen
- Cellular therapy like Idecabtagene vicleucel
- Glucocorticoids like Dexamethasone or Prednisone

Prognosis

Medial survival ranges from 30 to 60 months, with some advanced diagnoses surviving for no more than 6 months

Strengtheners

any of the treatments mentioned above, use of imaging and specific bloods also mentioned above

Preliminary code list

Condition domain

concept_id	concept_name
437233	Multiple myeloma
37016161	Light chain nephropathy due to multiple myeloma
37209514	Hypogammaglobulinemia due to multiple myeloma
4043713	Neuropathy due to multiple myeloma
4224628	Amyloid light chain amyloidosis due to multiple myeloma
4258135	Asymptomatic multiple myeloma

4259972	Indolent multiple myeloma
764229	Relapse multiple myeloma
42538151	Osteoporosis co-occurrent and due to multiple myeloma
436059	Multiple myeloma in remission
4019477	Myeloma-associated amyloidosis
4082464	Light chain myeloma
4079684	Non-secretory myeloma
4111355	IgA myeloma
4111356	IgG myeloma
4112310	IgD myeloma
4197600	Lambda light chain myeloma
4137433	Myeloma kidney
4188299	Kappa light chain myeloma
4137510	Osteosclerotic myeloma
4145040	Solitary osseous myeloma
133158	Plasma cell leukemia in remission
760936	Plasma cell leukemia in relapse
133154	Plasma cell leukemia

Observation domain

concept_id	concept_name
46270015	History of multiple myeloma
4210177	Multiple myeloma

Chronic lymphocytic leukaemia

Clinical description

Overview

Chronic lymphocytic leukemia (CLL) is a neoplasm characterized by the proliferation and accumulation of lymphocytes, usually B lineage, immunoincompetent. It is characterized by an invasion of peripheral and medullary blood by lymphocytes, and is of low aggressiveness. It is the most common form of leukemia in Western countries, it occurs in adulthood (median: 65 years) with a slight predominance in males.

Presentation

In 70% of cases it presents asymptomatically (incidental finding of lymphocytosis).

The clinical manifestations of this disease are due to the progressive infiltration of the bone marrow, lymph nodes and other tissues by lymphocytes, and to immunological alterations.

- B symptoms (fever, weight loss, night sweats).
- Anemic syndrome: it can be due to three causes: pure red cell aplasia of infiltrative origin, autoimmune hemolytic anemia (Coombs +), and hypersplenism.
- Infections (mainly bacterial and pulmonary, but also due to herpes viruses and opportunistic germs): due to alterations in immunity (hypogammaglobulinemia) and are the main cause of death.
- Thrombopenia (MIR): infiltrative or autoimmune origin.
- Bilateral and symmetric adenopathies.
- Splenomegaly and hepatomegaly.
- Infiltration of other tissues (skin, kidney, lung, CNS): exceptional.
- Increased risk of second neoplasms (carcinoma of the skin, digestive tract and lung) and autoimmune phenomena.

Assessment

Analytical data

- Complete blood count and peripheral blood smear: leukocytosis, lymphocytosis (>85%, small lymphocytes with a mature appearance with Gümprecht shadows –lymphocytes ruptured due to excessive fragility–), anemia, thrombocytopenia.
- Bone marrow: >30% lymphocytes.
- Cytogenetics (alterations in 80% of cases): del (13q), trisomy 12,... Immunophenotype: of B lymphocytes (CD19+, CD22+) with co-expression of CD5, CD23, CD20 (weak).

Others: hypogammaglobulinemia (due to humoral immunodeficiency), ↑ LDH, positive direct Coombs test, ↑ β2microglobulin.

Diagnosis

- Sustained lymphocytosis (>5 × 109/l).
- Typical morphology (with <10% immature-looking).
- Compatible immunophenotype (CD5, CD19, CD20 –weak– and CD23).
- Bone marrow infiltration >30% and/or bone marrow biopsy compatible with CLL.

CLL is a very common entity, especially in elderly patients. Therefore, in the presence of lymphocytosis with conclusive flow cytometry in peripheral blood, the diagnosis is a fact and no further complementary studies will be required if the patient is asymptomatic and has no treatment criteria. Carrying out more complex

diagnostic techniques such as bone marrow biopsy, mutation studies, cytogenetics or imaging tests are only justified if the patient is symptomatic or meets treatment criteria.

Staging

BINET & RAI

Plan

Most asymptomatic patients are not treated.

Treatment onlyif there are symptoms or high grade:

- Chemotherapy: combinations with fludarabine, cyclophosphamide and rituximab (FCR).
- New inhibitors: BTK (ibrutinib), PI3K (idelalisib) or bcl2 (venetoclax) inhibitors. They are used both first line (especially in high-risk patients: p53 or del17p mutation), and in relapsed or refractory patients.
- Others: chlorambucil + rituximab/obinotuzumab, bendamustine + rituximab, transplant, etc. In patients with CLL who present with del17p or TP53, ibrutinib and idelalisib are approved as first line. These drugs are also approved in refractory or post-relapse CLL; It is important to review the security profile.
-

Prognosis

Bad prognosis factors:

Older patient, Binet B/C, Rai II-IV

Massive infiltration of bone marrow

Lymphocyte duplication time <12 months

del17p; del11q

High CD38 expression

High ZAP70 Expression

Not mutated IgVH

Mutated TP53/del17p

CLL can transform into pro-lymphocytic leukaemia (>55% peripheral blood prolymphocyte, poor prognosis) or in Richter syndrome (transformation to a high-grade large cell lymphoma). Exceptionally can lead to acute lymphoblastic leukaemia or myeloma multiple. Most patients die from the neoplasm itself and from the situation of humoral immunodeficiency (infections).

Preliminary code list

Condition domain

concept_id	concept_name
44811227	Clinical stage A chronic lymphocytic leukaemia
44811228	Clinical stage B chronic lymphocytic leukaemia
44814026	Clinical stage C chronic lymphocytic leukaemia
4082311	B-cell chronic lymphocytic leukemia
4173824	B-cell chronic lymphocytic leukemia variant
4173955	T-cell chronic lymphocytic leukemia

4082338	Chronic lymphocytic prolymphocytic leukemia syndrome
4297353	Leukemic infiltration of skin (chronic T-cell lymphocytic leukemia)
4326339	Smoldering chronic lymphocytic leukemia
37110902	Chronic lymphocytic leukemia genetic mutation variant
37206728	Monoclonal B-cell lymphocytosis chronic lymphocytic leukemia-type
760935	Chronic lymphoid leukemia in relapse
4188973	Chronic myeloid leukemia in lymphoid blast crisis
133438	Chronic lymphoid leukemia in remission
138379	Chronic lymphoid leukemia, disease
44783718	T-cell large granular lymphocytic leukemia
132570	Leukemic reticuloendotheliosis of lymph nodes of head, face and neck
4082460	Large granular lymphocytic leukemia
193429	Leukemic reticuloendotheliosis of intra-abdominal lymph nodes
4173974	B-cell prolymphocytic leukemia
132852	Leukemic reticuloendotheliosis of extranodal AND/OR solid organ site
4082459	Hairy cell leukemia variant
4299151	Leukemic infiltration of skin in hairy-cell leukemia
4001331	Prolymphocytic leukemia (clinical)
37312023	B-cell prolymphocytic leukemia in remission
4245460	Hairy cell leukemia of spleen
4139554	Atypical hairy cell leukemia
439269	Leukemic reticuloendotheliosis of lymph nodes of axilla and upper limb
4038845	Hairy cell leukemia (clinical)
318989	Leukemic reticuloendotheliosis of lymph nodes of multiple sites
4079683	T-cell prolymphocytic leukemia
4173956	Richter's syndrome
439268	Leukemic reticuloendotheliosis of lymph nodes of inguinal region and lower limb
196650	Leukemic reticuloendotheliosis of intrapelvic lymph nodes
4173957	Splenic lymphoma with villous lymphocytes
442095	Leukemic reticuloendotheliosis of intrathoracic lymph nodes

Observation domain

concept_id	concept_name
4180093	Chronic lymphocytic leukemia
46270567	History of chronic lymphocytic leukemia
37312112	Monoclonal B-cell lymphocytosis chronic lymphocytic leukemia-type
37312109	Monoclonal B-cell lymphocytosis non-chronic lymphocytic leukemia type
4186899	Chronic lymphoid leukemia - category

Acute myeloid leukaemia

Clinical description

Overview

Acute myeloid leukemia (AML) is the most common acute leukemia in older patients (median 65-70 y at diagnosis). Characterized by the infiltration of blood, bone marrow and sometimes other tissues by proliferative, poorly differentiated hematopoietic cells.

Presentation

Mostly presenting with nonspecific symptoms that begin gradually, or abruptly, and are the consequence of anemia, leukocytosis, leukopenia/leukocyte dysfunction, or thrombocytopenia, typically in the up to 3 months before diagnosis. Frequent symptoms include fatigue, fever, bleeding/haemorrhage, bruising, bone pain, cough, headache, excessive sweating/diaphoresis.

Physical examination could find signs of infection, retinal haemorrhage / papilledema, gum hypertrophy, splenomegaly, hepatomegaly, or lymphadenopathy. Thrombosis (stroke, MI, venous) or disseminated intravascular coagulation (DIC) can occur.

Blood tests could identify anaemia, leukocytosis or thrombocytopenia.

AML includes many subtypes, which we need to bear in mind for phenotyping purposes. This is the WHO 2016 classification for subtypes of AML:

Acute myeloid leukemia (AML) with recurrent genetic abnormalities

- AML with t(8;21)(q22;q22); RUNX1RUNX1T1
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFBMYH11
  Acute promyelocytic leukemia with P M LR
- A R A
- AML with t(9;11)(p21.3;q23.3); MLLT3KMT2A
- AML with t(6;9)(p23;q34.1); DEKNUP214
- AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
- AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15MKL1
- Provisional entity: AML with BCRABL1
- AML with mutated NPM1
- AML with biallelic mutations of CEBPA
- Provisional entity: AML with mutated RUNX1
  AML with myelodysplasia related changes
- Therapy related myeloid neoplasms
  AML, not otherwise specified (NOS)
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Pure erythroid leukemia

- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis
  Myeloid sarcoma
  Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis (TAM)
- Myeloid leukemia associated with Down syndrome

Assessment

Will include imaging of multiple sites e.g. spine or CNS MRI, or chest x-ray. Bloods and genetic tests. Bone marrow biopsy. HLA typing can be used to plan therapy/ies.

Plan

For younger patients, aggressive chemo with cytarabine and an anthracycline (e.g., daunorubicin, idarubicin) is the most commonly recommended treatment. Other agents can be added e.g., cladribine. Less treatment likely in those aged 60 or older, for whom benefit-risk is not clear. Sometimes other treatments are used in older or higher risk patients, e.g. decitabine, azacitidine, or clofarabine.

Sometimes, hematopoietic stem cell transplantation is necessary, typically in younger patients with a curative intention.

Prognosis

Long-term survival is infrequent, at about 1 in 4 in 5 years from diagnosis.

MedDRA PTs

n/a

Disqualifiers

n/a

Strengtheners

Genetic testing, genetic mutations, HLA mutation or assessments
Previous radiotherapy or chemotherapy for other cancers (rarely)
Age at diagnosis >60
Treatment with cytarabine, daunorubicin, idarubicin, decitabine, azacitidine, or clofarabine [if hospital rx are seen in data]
Hematopoietic stem cell transplantation

Preliminary code list

Condition domain

concept_id	concept_name
44807009	Acute myeloid leukaemia with 11q23 abnormality
3572249	Relapsing acute myeloid leukemia
3572256	Refractory acute myeloid leukemia
135499	Subacute myeloid leukemia
4233531	Acute myeloid leukemia, minimal differentiation, FAB M0

4230253	Acute myeloid leukemia without maturation, FAB M1
4234749	Acute myeloid leukemia with maturation, FAB M2
4300784	Leukemic infiltration of skin in acute myeloid leukemia
4143382	Subacute myeloid leukemia in remission
4138903	Acute myeloid leukemia with maturation, FAB M2, in remission
40481524	Acute myeloid leukemia with t(9:11)(p22;q23); MLLT3-MLL
40483761	Acute myeloid leukemia with myelodysplasia-related changes
764781	Acute myeloid leukemia, minimal differentiation, FAB M0 in remission
764782	Acute myeloid leukemia without maturation, FAB M1 in remission
45765495	Core binding factor acute myeloid leukemia
45766268	Cytogenetically normal acute myeloid leukemia
36715587	Acute myeloid leukemia due to recurrent genetic abnormality
36717461	Therapy related acute myeloid leukemia and myelodysplastic syndrome
37110870	Acute myeloid leukemia with t(8;16)(p11;p13) translocation
37116722	Acute myeloid leukemia with t(6;9)(p23;q34) translocation
42539431	Acute myeloid leukemia with FMS-like tyrosine kinase-3 mutation
42538579	Therapy related acute myeloid leukemia due to and following administration of antineoplastic agent
35622003	Acute myeloid leukemia with NPM1 somatic mutation
35607963	Megakaryoblastic acute myeloid leukemia with t(1;22)(p13;q13)
35622696	Acute myeloid leukemia with CEBPA somatic mutations
35622760	Inherited acute myeloid leukemia
35623630	Acute myeloid leukemia and myelodysplastic syndrome related to alkylating agent
35623631	Acute myeloid leukemia and myelodysplastic syndrome related to topoisomerase type 2 inhibitor
35623633	Acute myeloid leukemia and myelodysplastic syndrome related to radiation
36683269	Acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
3654662	Acute myeloid leukemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22) CBFB-MYH11
135762	Acute myeloid leukemia in remission
140352	Acute myeloid leukemia, disease
4326339	Smoldering chronic lymphocytic leukemia
4002497	Acute promyelocytic leukemia, FAB M3
4112803	Acute promyelocytic leukemia - hypogranular variant
4137687	Acute promyelocytic leukemia, FAB M3, in remission
36676614	Differentiation syndrome due to and following chemotherapy co-occurrent with acute promyelocytic leukemia
4175688	Hypergranular promyelocytic leukemia
4116880	Acute myelomonocytic leukemia - eosinophilic variant
44784490	Acute monoblastic leukemia in remission
140672	Acute monocytic leukemia in remission
4142105	Acute myelomonocytic leukemia, FAB M4, in remission
136930	Megakaryocytic leukemia in remission

4139358	Erythroleukemia, FAB M6 in remission
4079686	Acute megakaryoblastic leukemia
138099	Erythroleukemia, FAB M6
4144191	Basophilic leukemia
4003187	Acute myelomonocytic leukemia, FAB M4
135768	Acute monocytic leukemia
4003184	Acute panmyelosis with myelofibrosis
4082485	Acute monoblastic leukemia
4189938	Acute monocytic/monoblastic leukemia
4173970	Acute eosinophilic leukemia
132850	Myeloid leukemia in remission

Observation domain

concept_id	concept_name
4304355	Acute myeloid leukemia with abnormal marrow eosinophils
4304199	Acute myeloid leukemia, minimal differentiation
4304356	Acute myeloid leukemia without maturation
4304051	Acute myeloid leukemia with maturation
4029177	Acute myeloid leukemia with myelodysplasia-related changes
4028713	Acute myeloid leukemia, t(8;21) (q22;q22)
4029663	Acute myeloid leukemia, 11q23 abnormalities
4030263	Therapy-related acute myeloid leukemia and myelodysplastic syndrome
4031360	Acute myeloid leukemia, M6 type
4073533	Acute myeloid leukemia, no ICD-O subtype
4265011	Acute myeloid leukemia with recurrent genetic abnormality
4264447	Acute myeloid leukemia with multilineage dysplasia following a myelodysplastic syndrome or myelodysplastic syndrome/myeloproliferative disorder
4288090	Acute myeloid leukemia with multilineage dysplasia without antecedent myelodysplastic syndrome
4287472	Therapy-related acute myeloid leukemia and myelodysplastic syndrome, alkylating agent-related type
4265012	Therapy-related acute myeloid leukemia and myelodysplastic syndrome, topoisomerase type II inhibitor-related type
4184848	Acute myeloid leukemia
42872921	Mixed phenotype acute leukemia B/myeloid
42872922	Mixed phenotype acute leukemia T/myeloid
42872933	Acute myeloid leukemia with t(6;9)(p23;q34); DEK-NUP214
42872934	Acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
42872942	Acute myeloid leukemia (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
45771384	Acute myeloid leukemia with mutation of CEBPA (CCAAT enhancer binding protein alpha) gene
45766616	Acute myeloid leukemia with mutated NPM1

37110871	Acute myeloid leukemia with t(8;16)(p11;p13) translocation
42535969	Acute myeloid leukemia with FMS-like tyrosine kinase-3 mutation
37204375	Acute myeloid leukemia with BCR-ABL1
37204557	Acute myeloid leukemia with mutated RUNX1
37312067	Acute myeloid leukemia with biallelic mutation of CEBPA (CCAAT enhancer binding protein alpha) gene
46273391	History of acute myeloid leukemia

Acute lymphocytic leukaemia

Clinical description

Overview

Acute lymphocytic leukaemia (also called "ALL", acute "lymphoblastic" leukaemia) is a type of cancer that affects white blood cells. In ALL, the process of development of blood cells is faulted, with immature, non-functioning leukemic cells being released from hematopoietic progenitors in the bone marrow or lymphatic system. This leads to anaemia, granulocytopenia, and thrombocytopenia, and causes symptoms of fatigue, weakness, breathlessness, infection, and haemorrhage. ALL progresses quickly and aggressively, with immediate treatment being required.

ALL it is the most frequent neoplastic disease in children, with most of the cases being diagnosed in children aged 3-4 years. In adults, incidence ranges from 0.7 to 1.8/100 000 per year, being slightly higher in adolescents and young adults and the elderly.

Presentation

Common symptoms why patients first seeks medical advice include fatigue and feeling breathless, repeated infections over a short time and unusual and frequent bleeding. Other symptoms can comprise pale, easily bruised skin; high temperature and night sweats; bone and joint pain as well as swollen lymph nodes, abdominal pain and unintentional weight loss.

In some cases the central nervous system (CNS) is also affected, with neurological symptoms including headaches, seizures, blurred vision or dizziness being reported.

Assessment

- Peripheral blood counts: White blood cell (WBC) count in ~40% of ALL patients is reduced or normal. In 8% of ALL patients, no circulating leukemic blast cells were observed. Peripheral blood typically shows anaemia, thrombocytopenia, and neutropenia: Nearly 30% of patients have haemoglobin levels below 7–8 g/dL. Platelet counts below the critical number of 20 × 109/L and neutropenia (neutrophils <0.5 × 109/L), are each noted in ~20% of adults with ALL, respectively.
- Bone marrow biopsy: To assess immunologic, cytogenetic, and genomic markers. In ALL, the bone marrow is typically packed with leukemic blast cells with >90% in ~70% of patients, and normal hemopoietic elements are greatly reduced or absent.
- Lumbar puncture: CNS leukaemia is diagnosed if ≥5 cells/µL or leukemic blast cells were observed by morphology in cerebrospinal fluid. Lumbar puncture is conducted either when remission is achieved or before treatment starts, and restricted to patients with an adequate platelet count.
- Immunological assays for classification into B-cell lineage or T-cell lineage ALL leukaemias. B-Cell Lineage ALL: 70% of adult ALLs are of B-cell origin, T-Cell Lineage ALL: ~25% of adult ALLs are of T-cell

lineage, Biphenotypic or Mixed Leukaemia, which express markers of both lymphoid and myeloid lineages on the same leukemic cells

- Cytogenetic and molecular analyses to define ALL subtypes, typically via standard cytogenetics, fluorescence in situ hybridization, and reverse transcriptase polymerase chain reaction.

Plan

- Pre-phase therapy: glucocorticoids (alone or combination) for ~5–7 days
- Induction therapy: typically vincristine, glucocorticoids, anthracyclines with or without cyclophosphamide or cytarabine. Adult ALL: L-Asparaginase is the only ALL-specific drug, targeted therapies including Tyrosine-kinase inhibitors (TKI, e.g. imatinib, dasatinib, nilotinib, ponatinib) for Ph+ ALL, immunological therapies (e.g. rituximab, blinatumomab)
- Post-remission consolidation: six to eight courses of high-dose methotrexate and/or cytarabine
- Maintenance treatment: 6-mercaptopurine and methotrexate plus intrathecal therapy, typically for 2–2.5 years. For Ph+ ALL maintenance includes TKI
- Stem Cell Transplantation is an essential part of the treatment strategy for adult ALL for high-risk patients.

Prognosis

Highly age-related, with cure rates of ~90% in children, decreasing to <10% in elderly or frail patients

MedDRA PTs

N/A

Disqualifiers

N/A

Strengtheners

- Minimal residual disease (MRD) during therapy
- Stem cell transplantation
- Diagnosis in young children
- previous chemotherapy, genetic disorders e. g. Down Syndrome, weakened immune system (HIV, AIDS)

Preliminary code list

Condition domain

concept_id	concept_name
36712834	Acute lymphoid leukemia relapse
36712835	Refractory acute lymphoid leukemia
136656	Subacute lymphoid leukemia
4139054	Subacute lymphoid leukemia in remission
37018868	Disorder of central nervous system co-occurrent and due to acute lymphoid leukemia in remission
37018869	Disorder of central nervous system co-occurrent and due to acute lymphoid leukemia
141816	Acute lymphoid leukemia in remission
134305	Acute lymphoid leukemia

4173963	B-cell acute lymphoblastic leukemia
4082461	Precursor B-cell acute lymphoblastic leukemia
4079280	Common acute lymphoblastic leukemia
4079281	Null cell acute lymphoblastic leukemia
4082462	T-cell acute lymphoblastic leukemia
4153344	Acute lymphoblastic leukemia, transitional pre-B-cell
4299143	Leukemic infiltration of skin (T-cell lymphoblastic leukemia)
4221907	Precursor T cell lymphoblastic leukemia/lymphoblastic lymphoma
4138008	Philadelphia chromosome-positive acute lymphoblastic leukemia
4138752	Precursor B-cell acute lymphoblastic leukemia in remission
4143997	T-cell acute lymphoblastic leukemia in remission
37017893	Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia
37109936	B lymphoblastic leukemia lymphoma with t(9:22) (q34;q11.2); BCR-ABL 1
3654647	B lymphoblastic leukemia lymphoma with t(5;14)(q31;q32); IL3-IGH
3654648	B lymphoblastic leukemia lymphoma with t(v;11q23); MLL rearranged
3654649	B lymphoblastic leukemia lymphoma with t(12;21) (p13;q22); TEL/AML1 (ETV6-RUNX1)
3654650	B lymphoblastic leukemia lymphoma with t(1;19)(Q23;P13.3); E2A-PBX1 (TCF3/PBX1)
3654651	B lymphoblastic leukemia lymphoma with hypodiploidy
3654653	B lymphoblastic leukemia lymphoma with hyperdiploidy
4003188	Adult T-cell leukemia/lymphoma
4081867	Acute biphenotypic leukemia
4227963	Precursor T-cell lymphoblastic lymphoma
134596	Lymphoid leukemia in remission

Observation domain

concept_id	concept_name
4030260	Precursor cell lymphoblastic leukemia
4029662	Precursor B-cell lymphoblastic leukemia
4030261	Precursor T-cell lymphoblastic leukemia
4264448	Precursor B-lymphoblastic leukemia/lymphoblastic lymphoma
4288091	Precursor T cell lymphoblastic leukemia/lymphoblastic lymphoma
4189936	Acute lymphoblastic leukemia - category
4143821	Philadelphia chromosome-positive acute lymphoblastic leukemia
42872925	B lymphoblastic leukemia / lymphoma - category
42872954	B lymphoblastic leukemia lymphoma, no ICD-O subtype
42872955	B lymphoblastic leukemia lymphoma with t(9;22)(q34;q11.2); BCR-ABL1
42872956	B lymphoblastic leukemia lymphoma with t(v;11q23); MLL rearranged
42872957	B lymphoblastic leukemia lymphoma with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1)
42872958	B lymphoblastic leukemia lymphoma with hyperdiploidy
42872959	B lymphoblastic leukemia lymphoma with hypodiploidy (Hypodiploid ALL)

42872960	B lymphoblastic leukemia lymphoma with t(5;14)(q31;q32); IL3-IGH
42872961	B lymphoblastic leukemia lymphoma with t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1)
45766617	T lymphoblastic leukemia/lymphoma
37204662	NK-lymphoblastic leukemia/lymphoma
37204838	B-lymphoblastic leukemia lymphoma BCR-ABL1-like
37206196	B lymphoblastic leukemia lymphoma with iAMP21

Appendix II: ENCePP checklist for study protocols

Study title:
Drug utilisation of valproate-containing medicinal products in women of childbearing potential

EU PAS Register® number: N/A
Study reference number (if applicable): N/A

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]			X	5
1.1.2 End of data collection[3]			X	
1.1.3 Progress report(s)			X	
1.1.4 Interim report(s)			X	
1.1.5 Registration in the EU PAS Register®			X	
1.1.6 Final report of study results.			X	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X			6, 7
2.1.2 The objective(s) of the study?	X			
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X			
2.1.4 Which hypothesis(-es) is (are) to be tested?			X	
2.1.5 If applicable, that there is no *a priori* hypothesis?			X	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	X			8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X			8.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	X			8.8
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio,			X	

	hazard ratio, risk/rate difference, number needed to harm (NNH))				
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)			X	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	X			8.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	X			8.5
	4.2.2 Age and sex	X			
	4.2.3 Country of origin	X			
	4.2.4 Disease/indication	X			
	4.2.5 Duration of follow-up	X			
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X			8.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)			X	
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)			X	
5.3	Is exposure categorised according to time windows?			X	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)			X	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?			X	
5.6	Is (are) (an) appropriate comparator(s) identified?			X	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**

6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	X			8.6.2
6.2	Does the protocol describe how the outcomes are defined and measured?	X			8.6.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)			X	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)			X	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)			X	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)			X	
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)			X	

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	X			8.8

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)			X	
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	X			8.2
	9.1.3 Covariates and other characteristics?	X			8.2
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)			X	

	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)			X	
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X			8.6
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)			X	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	X			8.6
	9.3.3 Covariates and other characteristics?	X			8.6
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)			X	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	X			8.8
10.2 Is study size and/or statistical precision estimated?			X	
10.3 Are descriptive analyses included?	X			8.8
10.4 Are stratified analyses included?	X			8.8
10.5 Does the plan describe methods for analytic control of confounding?			X	
10.6 Does the plan describe methods for analytic control of outcome misclassification?			X	
10.7 Does the plan describe methods for handling missing data?			X	
10.8 Are relevant sensitivity analyses described?	X			8.8

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	X			9
11.2 Are methods of quality assurance described?	X			10
11.3 Is there a system in place for independent review of study results?			X	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				

12.1.1 Selection bias? 12.1.2 Information bias? 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).			X X X	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	X			8.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	X			13
13.2 Has any outcome of an ethical review procedure been addressed?			X	
13.3 Have data protection requirements been described?	X			9.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	X			4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	X			14
15.2 Are plans described for disseminating study results externally, including publication?	X			14

Comments:

Name of the main author of the protocol: Edward Burn

Date: 01/11/2022

Signature: E. Burn