Epidemiology of chronic lymphocytic leukaemia in an Irish subpopulation with total case ascertainment: an additional tool for health economic planning

Chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) is the commonest B-cell malignancy affecting Caucasians, with a variable national incidence depending on the ethnic composition and age profile of the population.[1] The National Cancer Registry of Ireland (NCRI) quotes a Republic of Ireland (ROI) CLL incidence of 6·1/100 000, which appeared lower than our clinical experience indicated.[2] Establishing accurate CLL incidence figures and numbers of patients requiring therapy would improve health service provision planning.

Chronic lymphocytic leukaemia is a clinically variable disease; up to one-third of patients are never treated, while 'high-risk' patients require costly, prolonged targeted therapy to circumvent chemoresistance.[3–5] Although unmutated immunoglobulin variable heavy chain (*IgVH*), tumour protein p53 (*TP53*), splicing factor 3B subunit 1 (*SF3B1*), baculoviral IAP repeat-containing 3 (*BIRC3*) and Notch receptor 1 (*NOTCH1*) gene mutations confer inferior outcomes, the commonly used targeted therapies that include Bruton tyrosine kinase inhibitors such as ibrutinib and the B-cell lymphoma 2 (BCL2) inhibitor, venetoclax are only available for *TP53*-disrupted (mutation or deletion) and relapsed CLL.[6,7] The high cost of these drugs is challenging for healthcare budgeting because of the requirement for long-term treatment until toxicity/resistance and the potential for multiple targeted drug combinations.

The present study uses a subpopulation 'complete ascertainment' approach to define the incidence of CLL and the numbers of patients requiring treatment annually in the ROI, many of whom may benefit from targeted-therapy treatment in first and second line as being defined by recently completed or ongoing studies.[8–10]

Methods

This multicentre, cross-sectional study was conducted from the 1 October 2017 to 30 September 2018 across St James's Hospital/Trinity College Dublin (population 250 000), University Hospital Limerick (population 473 000) and the Midlands Regional Hospital, Tullamore (population 349 233), with a total population of one million.[11,12] All newly diagnosed cases of CLL (Group A) and previously diagnosed CLL cases requiring treatment within 3 months (Group B) were identified by the regional flow cytometry service. Cluster of differentiation (CD)19, CD22, CD79b, CD23, CD5, Flinders Medical Centre-7 marker (FMC7), surface membrane Ig (SmIg) and the modified Matutes scoring system identified CLL with a ≥4 score.[13] Bone marrow and lymph-node biopsies were not included thereby excluding SLL. Ethics approval was granted and written informed consent was given for biobanking, an extended flow cytometry panel and *TP53* analysis. If consent was not provided, those patients were included for epidemiological purposes only. Flow cytometry was performed using a BD FACS CANTO II flow cytometer (BD Biosciences, San Jose, CA, USA). *TP53* mutational analysis was performed by next-generation sequencing. All pathogenic variants with >5% variant allelic frequency were reported. Cytogenetic results on del(17p) were available for Group B only.

Results

A total of 148 patients (Group A, 111; Group B, 37) were identified, resulting in an incidence of 11·1/100 000 and 4·1/100 000 requiring treatment. See Table I for demographic, Binet stage and *TP53* mutation results. Written consent was unavailable for 27 (18·2%) patients because of non-CLL associated ill health/death (11/27), cognitive impairment (2 of 27), patient wishes (7 of 27) and unknown (7 of 27).

In all, 142 (95.9%) were $CD5^+/19^+$ and 147 (99.3%) were $CD23^+$. Five were $CD5^-$ and a further patient was confirmed on marrow immunophenotype as the initial blood immunophenotype was $CD5^-$ and $CD23^-$, confirming a Matutes score of ≥4 in all cases.

In Group A, 4 of 111 (3·6%) required treatment within the study period of whom one was *TP53* mutated. In Group B, 25/37 (67·6%) were treatment naïve of whom two had a del(17p) and none had a *TP53* mutation. In all, 12/37 (32·4%) had been previously treated of whom one had both a *TP53* mutation and del(17p), one had del(17p) and three had *TP53* mutations. Therefore, 15 patients (Group A, one; Group B, 14) were eligible for targeted therapy i.e. 1·5/100 000.

Discussion

The demographic, Binet stage, immunophenotype and *TP53* disruption incidence is similar to other unselected, published CLL cohorts.[3–5] Our present incidence of 11·1/100 000 is

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Demographic and clinical characteristics	All patients $N = 148$	Group A $n = 111$	Group B $n = 37$
Men, *n* (%)	102 (68·9)	76 (68·5)	26 (70·3)
Women, *n* (%)	46 (31·1)	35 (31·5)	11 (29·7)
Age diagnosis, years, median (range)	67·5 (29–91)	69 (41–91)	60 (29–79)
Binet Stage A, *n/N* (%)	97/148 (65·6)	94/111 (84·7)	3/37 (8·1)
Binet Stage B, *n/N* (%)	28/148 (18·9)	14/111 (12·6)	14/37 (37·8)
Binet Stage C, *n/N* (%)	23/148 (15·5)	3/111 (2·7)	20/37 (54·1)
TP53 mutated, *n/N* (%)	12/121 (9·9)	8/87 (9·2)	4/34 (11·8)
*17p*Del, *n/N* (%)	4/36 (11·1)	*N/A	4/36 (11·1)

Table I. Baseline and molecular characteristics of the study population.

*N/A, results not available for Group A.

based on recording consecutive newly diagnosed CLL cases by a centralised flow cytometry service and is almost double the NCRI incidence of 6·1/100 000, who base their incidence on inpatient and pathology data.[2] The total number of patients requiring CLL treatment annually was 4·1/100 000 (1·5/100 000 eligible for targeted therapies), which is closer to the NCRI incidence figures, reflecting the likely exclusion of the 'watch and wait' group by the NCRI and highlights the importance of customising cancer incidence collection to individual tumour diagnostic pathways. CLL incidence varied by centre, Dublin's inner-city area with a predominantly elderly population had the highest incidence (15·6/100 000) compared to the Midlands region (6·6/100 000) reflecting the young population living in Dublin's commuter belt, the incidence in the Midwest (10·3/100 000) reflects the mixed urban and rural populations in this region.[11] This snapshot of CLL incidence reflects the power of this type of study to plan healthcare services in different parts of a country.

The high CLL incidence identified in the present study may reflect the ROI population; the numbers aged >65 years have increased by 19·1% between 2011 and 2016.[11] Ireland has become ethnically diverse over the past 25 years, reflecting immigration of young people (aged <30 years) not typically affected by CLL, whereas those aged >65 years are predominantly Caucasian.[1,11] The determination of incidence based on flow cytometry uses the Haematological Malignancy Research Network (HMRN) methodology, who quote a 7·1/100 000 CLL incidence; we postulate that the more ethnically diverse older population in the HMRN network may partly explain their lower incidence figures.[14,15] General practice referral patterns to haematology services vary internationally, the approach in the ROI is based on annual blood checks and patients with a sustained lymphocytosis of $>5 \times 10^9$/l are referred to haematology, analysed by flow cytometry and are diagnosed at an early usually pre-symptomatic stage.

In conclusion, the present snapshot study with complete case ascertainment highlights the need for the national system of CLL incidence collection to change to a system based on flow cytometry diagnoses. The 'gold standard' of systematic disease data collection requires a national healthcare system and unique patient numbering system; however, complete CLL case ascertainment in a defined subpopulation with immunophenotyping as the diagnostic criteria has allowed us to establish accurate data that can be used by healthcare economists.

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Ethics

All procedures followed were in accordance with the ethical standards of the St. James's Hospital ethical committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Consent

All patients that had *TP53* analysis and biobanking performed gave written informed consent before inclusion in the study. In cases where consent was not provided, biobanking and molecular analysis were not performed, and these patients were included for epidemiology purposes only.

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Conflict of interest

The authors declare no conflict of interests, financial or otherwise.

Code availability

Not applicable.

Author contributions

Elisabeth Vandenberghe designed the study, analysed and interpreted the results and critically reviewed the manuscript. Carmel Waldron collated and analysed the data and wrote the manuscript. Sarah Brophy, Kanthi Perera, Gerard M. Crotty, Eoghan Dunlea, Aileen Walsh, Ashique Khan, Michelle Connolly, Ruth Clifford and Hilary O'Leary collected the data and provided valuable assistance in the design of the study. Kanthi Perera, Gerard M. Crotty, Eoghan Dunlea, Aileen Walsh, Michelle Connolly, Ruth Clifford, Hilary O'Leary, Giao Le, Christopher L. Bacon, David O'Brien, Emer Atkinson, Sarah Brophy, Greg Lee, Alexander Gillett and Fiona Quinn reviewed the manuscript. Emer Atkinson and Fiona Quinn did the molecular analysis while David O'Brien performed the flow cytometric analysis. Anthony M. McElligott was responsible for biobanking.

Data availability statement

The data from this study are available from the corresponding author (Carmel Waldron) upon request.

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