
Chronic lymphocytic leukaemia in Norway – incidence and prognostic markers at diagnosis

ORIGINAL ARTICLE

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Background.

The clinical courses of chronic lymphocytic leukaemia (CLL) are very heterogeneous. Biological markers that provide good prognostic information at the time of diagnosis are available. The aim of the study was to determine the prevalence of these markers in

a population-based material.

Material and method.

Biological markers were examined using standard laboratory methods after obtaining an informed consent statement from patients diagnosed with chronic lymphocytic leukaemia in the period 1.10.2007 – 31.12.2009.

Results.

There were 388 new cases of chronic lymphocytic leukaemia during the study period, and 236 patients (61 %) were included in the study. Of 222 patients, 178 (80 %) were in Binet's stage A, 26 (12 %) in stage B and 18 (8 %) in stage C. The V_H gene was mutated in 69 % and unmutated in 31 % of cases. Cytogenetic aberrations were found in 68 %: del(13q14) in 48 %, trisomy 12 in 13 %, del(11q22) in 10 % and del(17p13) in 7 %. CD38-positive disease was found in 28 % of the patients. The V_H gene was mutated in 67 % of the patients in Binet's stage A, and in the majority of these a mutated V_H gene was associated with non-expression of CD38 and del(13q14).

Interpretation.

At the time of diagnosis, most patients are asymptomatic and do not need treatment. The biological markers that indicate a favourable prognosis occur most frequently in this group. Markers that indicate a poor prognosis occur more frequently in the group that has symptoms at the time of diagnosis.

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia in Norway. A Norwegian study from the late 1990s indicated an incidence of almost 4/100 000 inhabitants per year, with a male-female ratio of 1.5; the median age at the time of diagnosis was 72 years at which time 78 % of the patients were asymptomatic (1). The clinical courses of chronic lymphocytic leukaemia are very variable. The extremes are rapidly progressing disease that responds poorly to treatment and results in death in the course of 2 – 3 years (5 – 10 % of patients) and indolent disease that never requires treatment and in exceptional cases goes into spontaneous remission (2, 3).

The disease stage is a good indicator of extent of disease and provides prognostic information at group level, but has proved unsuitable for applying a prognosis at individual level to asymptomatic patients. Over the past ten years we have gained considerable insight into pathophysiological factors, and several biological markers have proved useful for applying a prognosis to individual patients at the time of diagnosis. The most established prognostic markers are the mutational status of the gene that codes for the variable part of the immunoglobulin's heavy chain, the V_H, which the CLL cells use, cytogenetic aberrations and cell surface expression of CD38 (Box1) (4) – (7). The aim of the study in question was to survey the prevalence of these markers at the time of diagnosis in an unselected Norwegian patient material.

Box 1

Median survival from the time of diagnosis with different biological

markers (4 – 7)

- Unmutated V_H gene – 95 months
 - Mutated V_H gene – 293 months
 - del(17p13) – 32 months
 - del(11q22) – 79 months
 - Trisomy 12 – 114 months
 - No cytogenetic aberration – 111 months
 - del(13q14) – 133 months
 - CD38 positivity – 120 months
 - CD38 negativity – same as the age-adjusted general population
-

Material and method

Patient population

All those diagnosed with chronic lymphocytic leukaemia in the period 1.10. 2007 – 31.12. 2009 were invited to take part in the study. The patients were informed of the study by the doctor responsible for the care of the patient, and they were included after signing a statement of informed consent. The required patient data were sent together with an ordinary cancer notification to the Cancer Registry of Norway, which functioned as the secretariat for the study. In those cases where the Registry received notification of a new case of chronic lymphocytic leukaemia without the patient being included in the study, the doctor who had sent the notification was sent a written request to ask whether the patient would consent to inclusion. All contact with patients took place through the doctor responsible for the care of the patient.

The study was a cooperative project between the Norwegian Society of Haematology and the Cancer Registry. Norwegian haematologists were informed of the study through the Norwegian Society of Haematology, and detailed information about the study was available on the Society's and on the Cancer Registry's websites.

The study was approved by the Regional Committee of Medical Research Ethics (REK S-06353b) and the Norwegian Data Inspectorate (07/00254 – 2).

Diagnostic criteria

In order to make the diagnosis of chronic lymphocytic leukaemia, it was necessary to document persistent clonal B-lymphocytosis ($\geq 5 \cdot 10^9/l$) with a characteristic immunophenotype according to international guidelines (8). Small-cell lymphocytic lymphoma (SLL) is only distinguished from chronic lymphocytic leukaemia by the absence of leukaemia phenotype. Patients with clonal B-lymphocytosis, but $< 5 \cdot 10^9/l$, lymph node tumour and/or splenomegaly and characteristic histological findings in lymph nodes and/or bone marrow, were included under the diagnosis small-cell lymphocytic lymphoma.

The stage of the disease was determined on the basis of Binet's staging system. It was based on a clinical examination and determination of the haemoglobin and thrombocyte level (Table 1).

Table 1

Binet's classification of chronic lymphocytic leukaemia in stages (9)

Stage	Involved lymphoid organs ¹	Haemoglobin (g/100 ml)	Thrombocytes ($\cdot 10^9/l$)
A	< 3	≥ 10	≥ 100
B	> 3	≥ 10	≥ 100
C	No significance	< 10^2	< 100^2
[i]			

[i] ¹ Five relevant lymphoid organs – cervical, axillary, inguinal, splenic and hepatic lymph nodes

² One or both aberrations present

Flow cytometry

Immunophenotyping was performed using flow cytometry. Four-colour analysis of lymphocytes in blood was carried out after labelling with antibodies, lysis of erythrocytes and cell wash, as previously described (10). The percentage of CD38-positive CLL cells was determined from the fluorescence of the sample in question less the fluorescence of the control sample. CD38 positivity was defined as ≥ 20 % positive CLL cells.

Molecular genetics

The gene that coded for the variable part of the immunoglobulin's heavy chain (the V_H gene) in the CLL cells was identified by sequencing, and the gene's mutational status was investigated using DNA-based technology (11, 12). The V_H gene was characterised as unmutated at ≥ 98 % homology with the germline sequence and as mutated at < 98 % homology with the germline sequence (4, 5). Genomic polymerase chain reaction (PCR) was used to amplify the rearranged V_H gene.

Cytogenetics

The prevalence of cytogenetic aberrations was investigated by karyotyping short-term cultures of bone marrow cells (G-banding of metaphase chromosomes) and/or with interphase fluorescent in situ hybridisation (FISH) testing of blood cells or bone marrow cells using standard methods. The FISH results were classified as no cytogenetic aberrations, trisomy 12, del(6q23), del(11q22), del(13q14) or del(17p13) as the only aberration or in combinations (two or more aberrations found in the same patient).

Statistical methods

Descriptive statistics were used with a specification of median, average, spread and ratio. Chi-squared testing was used to show correlation between biological markers. Age-adjusted incidence was calculated on the basis of the standard population in the USA in the year 2000 because we had no data from any Norwegian population.

Results

The patients

During the study period, 388 new cases of chronic lymphocytic leukaemia were reported to the Cancer Registry. This is an incidence of 3.6/100 000/year (4.8 million inhabitants in Norway 2009 – 2010). This is equivalent to an age-adjusted incidence of 3.8/100 000/year. 236 of these patients (61 %) were included in the study, and eight of these were classified under small-cell lymphocytic lymphoma. Of those included, 139 were men and 97 women, i.e. a male-female ratio of 1.43.

The stage classification is shown in Table 2. The average age at the time of diagnosis was 65.9 (median 65.0). The age of those who were not included in the study was generally higher – average age 72.1 (median 73.0) – and the male-female ratio was 1.66. The majority of the patients were in stage A and the average values for haemoglobin were accordingly 13.5 g/100 ml (median 13.9 g/100 ml; spread 5.1 – 17.5 g/100 ml), lymphocytes $31 \cdot 10^9/l$ (median $16.5 \cdot 10^9/l$, spread $1.4 - 232 \cdot 10^9/l$) and thrombocytes $210 \cdot 10^9/l$ (median $211 \cdot 10^9/l$, spread $29 - 432 \cdot 10^9/l$).

Table 2

Correlation between clinical stage, V_H gene, immunophenotype and cytogenetic aberration with chronic lymphocytic leukaemia

	Patients	V _H gene mutated	V _H gene unmutated	Not available
	No. (%)	No. (%)	No. (%)	No. (%)
Stage classification	222			
Binet A	178 (80)	120 (67)	28 (16)	30 (17)
Binet B	26 (12)	7 (27)	16 (62)	3 (11)
Binet C	18 (8)	5 (28)	12 (67)	1 (6)
Immunophenotype	211			
CD38-positive	59 (28)	18 (31)	34 (58)	7 (12)
CD38-negative	152 (72)	109 (72)	19 (13)	23 (15)
FISH analysis ¹	112			
No aberrations	36 (32)	22 (61)	7 (19)	7 (19)
del(13q14)	53 (47)	35 (66)	13 (25)	2 (4)
Trisomy 12	15 (13)	5 (33)	8 (53)	2 (14)
del(11q22)	11 (10)	4 (36)	7 (64)	0
del(17p13)	8 (7)	3 (38)	3 (38)	2 (25)
Karyotyping	4			
t(14; 18)(q32; q21)	3	2 (67)	1 (33)	
t(11; 14)(q13; q23)	1		1	

	Patients	V _H gene mutated	V _H gene unmutated	Not available
	No. (%)	No. (%)	No. (%)	No. (%)
del(14q22)	1			1
[i]				

[i] ¹ Fluorising in situ hybridisation

Immunophenotyping

In 228 patients (97 %) the flow cytometry survey was complete enough for a CLL score according to Matutes et al. to be assigned (scale of 0 to 5) (13). The maximum score is 5 (score 5 = alternative diagnosis improbable, score 0 = alternative diagnosis probable). There were 192 patients with a score of 5, 25 with a score of 4, nine with a score of 3 and two with a score of 2. CD38 expression could be determined in 211 patients. 59 (28 %) had CD38-positive lymphocytic leukaemia and 152 (72 %) CD38-negative.

Molecular genetics

It was possible to identify the gene that coded for the variable part of the immunoglobulin's heavy chain in the CLL cells (preferred V_H gene) and to determine the mutational status of the V_H gene for 199 patients (84 %). 138 patients (69 %) had a mutated V_H gene and 61 (31 %) an unmutated V_H gene. Two expressed V_H genes were identified in 18 patients (9 %), i.e. they had biallelic CLL. In 11 patients, one (three patients) or both (eight patients) of the V_H genes were unmutated and in seven both V_H genes were mutated.

In CLL, some V_H genes occur more frequently than others, and we found particularly frequent (> 10 patients) usage of the following genes: V_H1 – 69, V_H3 – 7, V_H3 – 23, V_H3 – 0 and V_H4 – 34.

Where V_H3 – 21 is the preferred V_H gene, the prognosis is poor – irrespective of the mutational status of this V_H gene (14). We found that V_H3 – 21 was the preferred IgV_H gene in eight patients (4 %). It was mutated in two and unmutated in six.

Cytogenetics

Cytogenetic testing with FISH was successful in 112 patients. In one patient the karyotype was determined by G-banding alone. Cytogenetic aberrations were not found in 36 patients (32 %), but they were found in 77 (68 %) (Table 2). Karyotyping with G-banding of 25 patients revealed t(14; 18)(q32; q21) in three, t(11; 14)(q13; q32) in one and del(14q22) in one.

The patient with t(11; 14)(q13; q32) had both CLL and mantle cell lymphoma, with about equally large cell populations as determined by flow cytometry analysis of the bone marrow. It is highly probable that the t(11; 14)(q13; q32) was associated with the mantle cell lymphoma because this translocation is characteristic of this lymphoma.

In 13 patients (12 %) the karyotype was characterised by more than one aberration. Three patients were found to have t(14; 18)(q32; q21), which is characteristic of follicular lymphoma. None of the three had lymph node tumours of any significance,

and in all three the tumour cells had characteristic CLL immunophenotype (CLL score 5) and other cytogenetic aberrations that are seen frequently with chronic lymphocytic leukaemia and not with follicular lymphoma.

Correlation between the various biological markers

The material showed conclusively that the various biological markers are correlated, but not in such a way that one marker can be used as a surrogate marker for one or more of the others. In patients in Binet's stage A, the preferred V_H gene was mutated in the majority, while the opposite was the case in patients in Binet's stage B and stage C ($p < 0.001$). CD38-positive CLL was associated with an unmutated and CD38-negative disease with a mutated V_H gene ($p < 0.001$).

In the case of cytogenetic changes that are associated with a favourable prognosis, the preferred V_H gene was most often mutated. The opposite was the case with del(11q22), which is associated with a poor prognosis. This is summed up in Table 2. Table 3 shows that it was not random whether the V_H gene was mutated or not in the different V_H gene uses. V_H1 – 69 occurred mainly unmutated; the opposite was the case for V_H4 – 34, V_H3 – 7 and V_H3 – 23.

Table 3

Mutational status of V_H genes that occur frequently in patients with chronic lymphocytic leukaemia

Preferred V _H gene	Number of patients	Mutated (%)	Unmutated (%)
V _H 1–69	18	28	72
V _H 3–7	20	90	10
V _H 3–23	16	94	6
V _H 3–30	20	65	35
V _H 4–34	25	80	20

Discussion

During the study period, the Cancer Registry registered 388 new cases of CLL, which is equivalent to an age-adjusted incidence of 3.8/100 000/year. This corresponds well with a recent American study, where an age-adjusted incidence of 3.83/100 000/year is reported, with a clear male dominance (15), but is somewhat lower than previously published Nordic studies which could indicate an incidence of 4/100 000/year (16, 17).

The primary aim of the study was to survey the involvement of biological markers with prognostic significance in an unselected material, and doctors were urged to carry out the tests in question on all recently diagnosed patients. This was done, if not fully, for those who were included. They were substantially younger than those who were not included (median 65 years, versus 73 years). The tests in question are quite resource-

and cost-intensive. It therefore seems likely that the doctors did not conduct these tests on the oldest patients because the result would not have consequences for the choice of treatment.

The failure to include mainly elderly patients has little impact on our calculations of the relative distribution of prognostic factors in the patient population because these factors do not show a different distribution in different age groups. There is a clear gender difference, however – high risk factors are seen more frequently in men than in women (4) – (6). Our project can nonetheless claim to be population-based and representative, but it is not unselected. The selection appears very largely to have been made by the doctors, because some geographical areas are not represented in the study, as in a previous study (1). Calculations of incidence and gender distribution were based on mandatory notifications to the Cancer Registry and were therefore carried out on an unselected material.

In the first studies that described the preferred V_H gene's mutational status in CLL there were almost equal numbers of patients with mutated and with unmutated V_H genes (4, 5). However, we found that 69 % of the patients had a mutated V_H gene and 31 % an unmutated gene. This is consistent with recently published, population-based studies from Europe and the USA (18, 19), which should indicate that our study is representative. The first reports came from specialised hospital departments, whereas our study and the more recent international studies are population-based and therefore cover a patient population that to a greater extent includes those with indolent disease, where we would expect CLL with a mutated V_H gene to predominate.

As early as in 1988, Kipps et al. described CLL cells as using a limited repertoire of V_H genes (20). These observations are confirmed in several studies, and a meta-analysis shows that the preferred V_H gene families associated with CLL differ from the repertoire of normal B-lymphocytes (21, 22). Our study is one more in the series.

CLL where both IgH genes are rearranged and expressed is well known. This is called biallelic CLL, as opposed to biclonal CLL, where two different CLL clones occur side by side (23, 24). The incidence of biallelic CLL has not been described previously. In our material, 9 % of the patients had biallelic CLL, and one or both of the preferred V_H genes were unmutated in the majority (61 %).

Like other investigators, we found that the CLL cells of just over a quarter of the patients expressed CD38 at the cell surface (19). CD38-positive CLL usually used an unmutated V_H gene (58 %), but CD38 expression cannot be used as a surrogate marker for the V_H gene's mutational status (7).

Hospitals report that about 80 % of patients have genetic aberrations in the CLL cells when they are tested for del(13q14), del(11q22), del(17p13) or trisomy 12 using FISH analysis, while about 20 % do not have cytogenetic aberrations (6). In our material, the percentage without cytogenetic aberrations is somewhat higher (33 %), but the distribution of the various cytogenetic aberrations is the same as that reported by others (Table 2). We found more than one cytogenetic aberration in 12 % of the patients. Others have pointed out that the prognosis of these patients is determined by the aberration associated with the poorest prognosis (6).

There may be a number of explanations for the somewhat higher proportion without cytogenetic aberrations in our material. Methodological factors that resulted in aberrations not being detected is one possibility, but if this were the explanation, we

would also have expected differences in the distribution of cytogenetic aberrations in relation to other materials. The cytogenetic aberrations in question are not regarded as primary pathogenetic events associated with chronic lymphocytic leukaemia; they come about along the way. One might therefore expect a higher proportion of patients without cytogenetic aberrations in a population-based material than in materials from specialist departments. One limitation of our material is that cytogenetic testing was conducted on a relatively low percentage of the patients (48 %).

The biological markers have strong prognostic significance, and may be of great assistance in providing prognostic information to the individual patient. This is particularly important because the bulk of the patients are diagnosed in an asymptomatic phase of the disease when treatment is not indicated. At present, treatment based on biological markers is not an option – with one exception: In the case of chronic lymphocytic leukaemia characterised by del(17p13) there is consensus that patients should receive treatment that is independent of the *p53* signal path (the *TP53* gene lies in chromosome band 17p13) in order to be effective (25). Immunochemotherapy (rituximab, fludarabine and cyclophosphamide) are considered today to be the optimal first-line treatment for CLL for those who tolerate aggressive therapy (age 70 or younger and no comorbidity). Immunochemotherapy is particularly effective with an unmutated *V_H* gene, del(13q14) and/or del(11q23) (26).

The article has been written on behalf of the Norwegian CLL study group.

Tabell

Main points
• Most patients with chronic lymphocytic leukaemia are asymptomatic at the time of diagnosis and are not to receive therapy • Most asymptomatic patients have a profile of biological markers that indicate a good prognosis • Two thirds of the patients have cytogenetic aberrations at the time of diagnosis • The preferred <i>V_H</i> gene is mutated in 69 % of the patients at the time of diagnosis

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